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Dated 20 November 2003

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P01/7700 0.00-0226434.9

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The Patent Office

Cardiff Road
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1. Your reference — 100892

2. Patent application number *(The Patent Office will fill in this part)* — 13 NOV 2002 — 0226434.9

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

AstraZeneca AB
S-151 85 Sodertalje
Sweden

Patents ADP number *(if you know it)* 07829448003

If the applicant is a corporate body, give the country/state of its incorporation — Sweden

4. Title of the invention

COMBINATION PRODUCT

5. Name of your agent *(if you have one)*

Brian Tait

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

AstraZeneca UK Limited
Global Intellectual Property
Mereside, Alderley Park
Macclesfield
Cheshire SK10 4TG

Patents ADP number *(if you know it)* 07966732002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

Patents Form 1/77

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Continuation sheets of this form	
Description	126
Claim(s)	02
Abstract	01
Drawing(s)	

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Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature Authorised Signatory Date 12/11/2002

12. Name and daytime telephone number of person to contact in the United Kingdom: Jennifer C Bennett - 01625 230148

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COMBINATION PRODUCT

The present invention relates to a combination comprising an inhibitor of the Src family of non-receptor tyrosine kinases, or a pharmaceutically acceptable salt thereof, and gemcitabine. The combination of the invention is useful in a new method for the treatment or prophylaxis of cancer. The invention also relates to a pharmaceutical composition comprising such a combination and to the use thereof in the manufacture of a medicament for use in the treatment or prophylaxis of cancer.

Current options for treating cancer include surgical resection, external beam radiation therapy and/or systemic chemotherapy. These are partially successful in some forms of cancer but are less successful in others. There is a clear need for new therapeutic treatments for treating cancer.

Many of the current treatment regimes for cell proliferation diseases such as cancer utilise compounds which inhibit DNA synthesis. Such compounds are toxic to cells generally but their toxic effect on rapidly dividing cells such as tumour cells can be beneficial. Alternative approaches to anti-tumour agents which act by mechanisms other than the inhibition of DNA synthesis have the potential to display enhanced selectivity of action.

In recent years it has been discovered that a cell may become cancerous by virtue of the transformation of a portion of its DNA into an oncogene i.e. a gene which, on activation, leads to the formation of malignant tumour cells (Bradshaw, Mutagenesis, 1986, 1, 91). Several such oncogenes give rise to the production of peptides which are receptors for growth factors. Activation of the growth factor receptor complex subsequently leads to an increase in cell proliferation. It is known, for example, that several oncogenes encode tyrosine kinase enzymes and that certain growth factor receptors are also tyrosine kinase enzymes (Yarden *et al.*, Ann. Rev. Biochem., 1988, 57, 443; Larsen *et al.*, Ann. Reports in Med. Chem., 1989, Chpt. 13). The first group of tyrosine kinases to be identified arose from such viral oncogenes, for example $pp60^{v\text{-}Src}$ tyrosine kinase (otherwise known as v-Src), and the corresponding tyrosine kinases in normal cells, for example $pp60^{c\text{-}Src}$ tyrosine kinase (otherwise known as c-Src).

Receptor tyrosine kinases are important in the transmission of biochemical signals which initiate cell replication. They are large enzymes which span the cell membrane and possess an extracellular binding domain for growth factors such as epidermal growth factor (EGF) and an intracellular portion which functions as a kinase to phosphorylate tyrosine

amino acids in proteins and hence to influence cell proliferation. Various classes of receptor tyrosine kinases are known (Wilks, Advances in Cancer Research, 1993, 60, 43-73) based on families of growth factors which bind to different receptor tyrosine kinases. The classification includes Class I receptor tyrosine kinases comprising the EGF family of receptor tyrosine kinases such as the EGF, TGFα, Neu and erbB receptors, Class II receptor tyrosine kinases comprising the insulin family of receptor tyrosine kinases such as the insulin and IGFI receptors and insulin-related receptor (IRR) and Class III receptor tyrosine kinases comprising the platelet-derived growth factor (PDGF) family of receptor tyrosine kinases such as the PDGFα, PDGFβ and colony-stimulating factor 1 (CSF1) receptors.

It is also known that certain tyrosine kinases belong to the class of non-receptor tyrosine kinases which are located intracellularly and are involved in the transmission of biochemical signals such as those that influence tumour cell motility, dissemination and invasiveness and subsequently metastatic tumour growth (Ullrich *et al.*, Cell, 1990, 61, 203-212, Bolen *et al.*, FASEB J., 1992, 6, 3403-3409, Brickell *et al.*, Critical Reviews in Oncogenesis, 1992, 3, 401-406, Bohlen *et al.*, Oncogene, 1993, 8, 2025-2031, Courtneidge *et al.*, Semin. Cancer Biol., 1994, 5, 239-246, Lauffenburger *et al.*, Cell, 1996, 84, 359-369, Hanks *et al.*, BioEssays, 1996, 19, 137-145, Parsons *et al.*, Current Opinion in Cell Biology, 1997, 9, 187-192, Brown *et al.*, Biochimica et Biophysica Acta, 1996, 1287, 121-149 and Schlaepfer *et al.*, Progress in Biophysics and Molecular Biology, 1999, 71, 435-478). Various classes of non-receptor tyrosine kinases are known including the Src family such as the Src, Lyn, Fyn and Yes tyrosine kinases, the Abl family such as Abl and Arg and the Jak family such as Jak 1 and Tyk 2.

It is known that the Src family of non-receptor tyrosine kinases are highly regulated in normal cells and in the absence of extracellular stimuli are maintained in an inactive conformation. However, some Src family members, for example c-Src tyrosine kinase, is frequently significantly activated (when compared to normal cell levels) in common human cancers such as gastrointestinal cancer, for example colon, rectal and stomach cancer (Cartwright *et al.*, Proc. Natl. Acad. Sci. USA, 1990, 87, 558-562 and Mao *et al.*, Oncogene, 1997, 15, 3083-3090), and breast cancer (Muthuswamy *et al.*, Oncogene, 1995, 11, 1801-1810). The Src family of non-receptor tyrosine kinases has also been located in other common human cancers such as non-small cell lung cancers (NSCLCs) including adenocarcinomas and squamous cell cancer of the lung (Mazurenko *et al.*, European Journal

of Cancer, 1992, 28, 372-7), bladder cancer (Fanning *et al.*, Cancer Research, 1992, 52, 1457-62), oesophageal cancer (Jankowski *et al.*, Gut, 1992, 33, 1033-8), cancer of the prostate, ovarian cancer (Wiener *et al.*, Clin. Cancer Research, 1999, 5, 2164-70) and pancreatic cancer (Lutz *et al.*, Biochem. and Biophys. Res. Comm., 1998, 243, 503-8). As further human tumour tissues are tested for the Src family of non-receptor tyrosine kinases it is expected that its widespread prevalence will be established.

It is further known that the predominant role of c-Src non-receptor tyrosine kinase is to regulate the assembly of focal adhesion complexes through interaction with a number of cytoplasmic proteins including, for example, focal adhesion kinase and paxillin. In addition c-Src is coupled to signalling pathways that regulate the actin cytoskeleton which facilitates cell motility. Likewise, important roles are played by the c-Src, c-Yes and c-Fyn non-receptor tyrosine kinases in integrin mediated signalling and in disrupting cadherin-dependent cell-cell junctions (Owens *et al.*, Molecular Biology of the Cell, 2000, 11, 51-64 and Klinghoffer *et al.*, EMBO Journal, 1999, 18, 2459-2471). Cellular motility is necessarily required for a localised tumour to progress through the stages of dissemination into the blood stream, invasion of other tissues and initiation of metastatic tumour growth. For example, colon tumour progression from localised to disseminated, invasive metastatic disease has been correlated with c-Src non-receptor tyrosine kinase activity (Brunton *et al.*, Oncogene, 1997, 14, 283-293, Fincham *et al.*, EMBO J, 1998, 17, 81-92 and Verbeek *et al.*, Exp. Cell Research, 1999, 248, 531-537).

Accordingly it has been recognised that an inhibitor of such non-receptor tyrosine kinases should be of value as a selective inhibitor of the motility of tumour cells and as a selective inhibitor of the dissemination and invasiveness of mammalian cancer cells leading to inhibition of metastatic tumour growth. In particular an inhibitor of such non-receptor tyrosine kinases should be of value as an anti-invasive agent for use in the containment and/or treatment of solid tumour disease.

It is stated in International Patent Applications WO 01/94341 and WO 02/16352 that the Src inhibitors disclosed therein may be administered as a sole therapy or may involve, in addition to the quinazoline derivatives of those inventions, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy was stated to include one or more of the following categories of anti-tumour agents :-

(i) other anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function);

(ii) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside and hydroxyurea, or, for example, one of the preferred antimetabolites disclosed in European Patent Application No. 562734 such as (2S)-2-{o-fluoro-p-[N-{2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzamido}-4-(tetrazol-5-yl)butyric acid); antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

(iii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene and iodoxyfene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrazole, vorazole and exemestane) and inhibitors of 5α-reductase such as finasteride;

(iv) inhibitors of growth factor function, for example such inhibitors include growth factor antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example the EGFR tyrosine kinase inhibitors N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (ZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (CP 358774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), for example inhibitors of the platelet-derived growth factor family and for example inhibitors of the hepatocyte growth factor family; and

(v) antiangiogenic agents such as those which inhibit vascular endothelial growth factor such as the compounds disclosed in International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354 and those that work by other mechanisms (for example linomide, inhibitors of integrin αvβ3 function and angiostatin).

There is no specific disclosure of the combination use of a Src inhibitor and the antimetabolite cytotoxic agent gemcitabine, nor that any such combination produces surprisingly effective results.

We have unexpectedly found that a particular selection from the generic disclosures of combination therapies mentioned in International Patent Applications WO 01/94341 and WO 02/16352 is very effective. In particular, the combination of an inhibitor of the Src family of non-receptor tyrosine kinases, or a pharmaceutically-acceptable salt thereof, (referred to on occasions hereinafter as a Src inhibitor) and gemcitabine produces surprisingly effective results. More specifically, the combination of a Src inhibitor and gemcitabine produces a greater effect than that achievable by the administration of either a Src inhibitor alone or gemcitabine alone.

According to the present invention there is provided a combination comprising an inhibitor of the Src family of non-receptor tyrosine kinases, or a pharmaceutically-acceptable salt thereof, and gemcitabine for use in the synergistic treatment or prophylaxis of cancer.

It is to be understood that term "a combination" envisages the simultaneous, separate or sequential administration of the components of the combination. In one aspect of the invention, "a combination" envisages simultaneous administration of the Src inhibitor and gemcitabine. In a further aspect of the invention, "a combination" envisages sequential administration of those agents. In another aspect of the invention, "a combination" envisages separate administration of those agents. Where the administration of those agents is sequential or separate, the delay in administering the second component should not be such as to lose the benefit of the synergistic effect of the combination therapy. Thus, for the avoidance of doubt, the present invention provides a combination comprising an inhibitor of the Src family of non-receptor tyrosine kinases, or a pharmaceutically-acceptable salt thereof, and gemcitabine for use simultaneously, sequentially or separately in the synergistic treatment or prophylaxis of cancer.

Suitable compounds possessing inhibitory activity against the Src family of non-receptor tyrosine kinases include the quinazoline derivatives disclosed in International Patent Applications WO 01/94341, WO 02/16352, WO 02/30924, WO 02/30926, WO 02/34744 and WO 02/085895 and the quinazoline and quinoline derivatives described in International Patent Applications PCT/GB 02/02117, 02/02124, 02/02128 & 02/03177.

Particular Src inhibitors include the following compounds from International Patent Application WO 01/94341 :-

4-(2-chloro-5-methoxyanilino)-5,7-di-(3-morpholinopropoxy)quinazoline,
4-(2-bromo-5-methoxyanilino)-7-methoxy-5-(N-methylpiperidin-4-yloxy)quinazoline,
4-(2-chloro-5-methoxyanilino)-7-methoxy-5-(N-methylpiperidin-4-yloxy)quinazoline,
4-(2-chloro-5-methoxyanilino)-7-[3-(4-methylpiperazin-1-yl)propoxy]-5-tetrahydropyran-4-yloxyquinazoline,
4-(2-chloro-5-methoxyanilino)-7-(3-morpholinopropoxy)-5-tetrahydropyran-4-yloxyquinazoline,
4-(2-chloro-5-methoxyanilino)-7-[2-hydroxy-3-(4-methylpiperazin-1-yl)propoxy]-5-tetrahydropyran-4-yloxyquinazoline,
4-(2-chloro-5-methoxyanilino)-7-(2-hydroxy-3-morpholinopropoxy)-5-tetrahydropyran-4-yloxyquinazoline,
4-(2-chloro-5-methoxyanilino)-7-[3-(4-methylpiperazin-1-yl)propoxy]-5-tetrahydrofuran-3-yloxyquinazoline,
4-(2-chloro-5-methoxyanilino)-7-(3-morpholinopropoxy)-5-tetrahydrofuran-3-yloxyquinazoline,
4-(5-chloronaphth-1-ylamino)-7-methoxy-5-(N-methylpiperidin-4-yloxy)quinazoline,
4-(3-chlorobenzofuran-7-ylamino)-7-methoxy-5-(N-methylpiperidin-4-yloxy)quinazoline,
7-benzyloxy-4-(2-bromo-5-methoxyanilino)-5-piperidin-4-yloxyquinazoline,
4-(2-bromo-5-methoxyanilino)-7-(3-methylsulphonylpropoxy)-5-piperidin-4-yloxyquinazoline,
4-(2-bromo-5-methoxyanilino)-7-methoxy-5-piperidin-4-ylmethoxyquinazoline,
4-(2,4-dichloro-5-methoxyanilino)-7-methoxy-5-(N-methylpiperidin-4-yloxy)quinazoline,
4-(2,5-dimethoxyanilino)-7-methoxy-5-(N-methylpiperidin-4-yloxy)quinazoline,
4-(2,4-dichloro-5-methoxyanilino)-7-(2-pyrrolidin-1-ylethoxy)-5-tetrahydropyran-4-yloxyquinazoline,
4-(2,4-dichloro-5-methoxyanilino)-7-(2-piperidinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline,
4-(2,4-dichloro-5-methoxyanilino)-7-(2-morpholinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline,
4-(2,4-dichloro-5-methoxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline,
4-(2-bromo-5-methoxyanilino)-7-(2-pyrrolidin-1-ylethoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(2-bromo-5-methoxyanilino)-7-(2-piperidinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(2-bromo-5-methoxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline,

4-(2-bromo-5-methoxyanilino)-7-(4-pyridyloxyethoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(2-bromo-5-methoxyanilino)-7-{2-[(2S)-2-(N,N-dimethylcarbamoyl)pyrrolidin-1-yl]ethoxy}-5-tetrahydropyran-4-yloxyquinazoline,

4-(2-bromo-5-methoxyanilino)-7-{2-[(2S)-2-(N-methylcarbamoyl)pyrrolidin-1-yl]ethoxy}-5-tetrahydropyran-4-yloxyquinazoline,

4-(2-bromo-5-methoxyanilino)-7-(4-pyridylmethoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(5-methoxy-2-pyrrolidin-1-ylanilino)-7-[3-(4-methylpiperazin-1-yl)propoxy]-5-tetrahydropyran-4-yloxyquinazoline,

4-(2-bromo-5-methoxyanilino)-5-cyclopentyloxy-7-(2-pyrrolidin-1-ylethoxy)quinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-5-cyclopentyloxy-7-(2-pyrrolidin-1-ylethoxy)quinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-5-piperidin-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-methoxy-5-piperidin-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-methoxy-5-(N-methylpiperidin-4-yloxy)quinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-methoxy-5-piperidin-4-ylmethoxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-(2-pyrrolidin-1-ylethoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-(3-pyrrolidin-1-ylpropoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-[3-(4-methylpiperazin-1-yl)propoxy]-5-tetrahydropyran-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-(2-piperidinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-pyridyloxy)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-piperidin-4-ylmethoxy-5-tetrahydropyran-4-yloxyquinazoline and

4-(6-chloro-2,3-methylenedioxyanilino)-7-(N-methylpiperidin-4-ylmethoxy)-5-tetrahydropyran-4-yloxyquinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

Further particular Src inhibitors include the following compounds from International Patent Application WO 02/16352 :-

6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-morpholinopropoxy)quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-[3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy]quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-piperidinopropoxy)quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-(N-methylpiperidin-4-ylmethoxy)quinazoline,

7-(2-hydroxy-3-pyrrolidin-1-ylpropoxy)-6-methoxy-4-(2,3-methylenedioxyanilino)-quinazoline,

7-[2-hydroxy-3-(N-isopropyl-N-methylamino)propoxy]-6-methoxy-4-(2,3-methylenedioxyanilino)quinazoline,

7-[3-(4-cyanomethylpiperazin-1-yl)-2-hydroxypropoxy]-6-methoxy-4-(2,3-methylenedioxyanilino)quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-{2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy}quinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-[3-(4-cyanomethylpiperazin-1-yl)propoxy]-6-methoxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,

4-(6-bromo-2,3-methylenedioxyanilino)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-[2-(N-methylpiperidin-4-yl)ethoxy]quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-[2-(4-pyridyloxy)ethoxy]quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-pyridylmethoxy)quinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-(2-cyanopyrid-4-ylmethoxy)-6-methoxyquinazoline and

4-(6-chloro-2,3-methylenedioxyanilino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

Further particular Src inhibitors include the following compounds from International Patent Application WO 02/30924 :-

4-(7-benzofuranylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,

4-(7-benzofuranylamino)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,

4-(7-benzofuranylamino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,

4-(7-benzofuranylamino)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,

4-(3-chlorobenzofuran-7-ylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,

4-(3-chlorobenzofuran-7-ylamino)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,

4-(3-chlorobenzofuran-7-ylamino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,

4-(3-chlorobenzofuran-7-ylamino)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,

4-(6-chlorobenzofuran-7-ylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,

4-(6-chlorobenzofuran-7-ylamino)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,

4-(6-chlorobenzofuran-7-ylamino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,

4-(6-chlorobenzofuran-7-ylamino)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,

4-(5-fluorobenzofuran-7-ylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,

4-(5-fluorobenzofuran-7-ylamino)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,

4-(5-fluorobenzofuran-7-ylamino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,

4-(5-fluorobenzofuran-7-ylamino)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,

4-(7-benzofuranylamino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline,

7-(2-acetoxy-3-pyrrolidin-1-ylpropoxy)-4-(3-chlorobenzofuran-7-ylamino)-6-methoxyquinazoline,

7-[2-acetoxy-3-(N-isopropyl-N-methylamino)propoxy]-4-(3-chlorobenzofuran-7-ylamino)-6-methoxyquinazoline,

7-[2-acetoxy-3-(4-cyanomethylpiperazin-1-yl)propoxy]-4-(3-chlorobenzofuran-7-ylamino)-6-methoxyquinazoline,

7-(2-acetoxy-3-piperidinopropoxy)-4-(3-chlorobenzofuran-7-ylamino)-6-methoxyquinazoline,
4-(3-chlorobenzofuran-7-ylamino)-7-(2-hydroxy-3-pyrrolidin-1-ylpropoxy)-6-methoxyquinazoline,
4-(3-chlorobenzofuran-7-ylamino)-7-[2-hydroxy-3-(N-isopropyl-N-methylamino)propoxy]-6-methoxyquinazoline,
4-(3-chlorobenzofuran-7-ylamino)-7-[3-(4-cyanomethylpiperazin-1-yl)-2-hydroxypropoxy]-6-methoxyquinazoline and
4-(3-chlorobenzofuran-7-ylamino)-7-(2-hydroxy-3-piperidinopropoxy)-6-methoxyquinazoline;
or a pharmaceutically-acceptable acid-addition salt thereof.

Further particular Src inhibitors include the following compounds from International Patent Application WO 02/30926 :-
4-(4-benzofuranylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
4-(4-benzofuranylamino)-7-[3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy]-6-methoxyquinazoline,
4-(4-benzofuranylamino)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,
4-(4-benzofuranylamino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,
4-(4-benzofuranylamino)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,
4-(4-benzofuranylamino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline,
4-(5-chlorobenzofuran-4-ylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
7-(2-acetoxy-3-pyrrolidin-1-ylpropoxy)-4-(3-chlorobenzofuran-4-ylamino)-6-methoxyquinazoline,
7-[2-acetoxy-3-(N-isopropyl-N-methylamino)propoxy]-4-(3-chlorobenzofuran-4-ylamino)-6-methoxyquinazoline,
7-[2-acetoxy-3-(4-cyanomethylpiperazin-1-yl)propoxy]-4-(3-chlorobenzofuran-4-ylamino)-6-methoxyquinazoline,
7-(2-acetoxy-3-piperidinopropoxy)-4-(3-chlorobenzofuran-4-ylamino)-6-methoxyquinazoline,
7-(2-acetoxy-3-morpholinopropoxy)-4-(3-chlorobenzofuran-4-ylamino)-6-methoxyquinazoline,
4-(4-benzofuranylamino)-7-(2-hydroxy-3-pyrrolidin-1-ylpropoxy)-6-methoxyquinazoline,
4-(4-benzofuranylamino)-7-[2-hydroxy-3-(N-isopropyl-N-methylamino)propoxy]-6-methoxyquinazoline,

4-(4-benzofuranylamino)-7-[3-(4-cyanomethylpiperazin-1-yl)-2-hydroxypropoxy]-6-methoxyquinazoline,

4-(4-benzofuranylamino)-7-(2-hydroxy-3-piperidinopropoxy)-6-methoxyquinazoline and

4-(4-benzofuranylamino)-7-(2-hydroxy-3-morpholinopropoxy)-6-methoxyquinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

Further particular Src inhibitors include the following compounds from International Patent Application WO 02/34744 :-

4-(7-indolylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,

4-(2,3-dimethylindol-7-ylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,

7-[3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy]-4-(7-indolylamino)-6-methoxyquinazoline,

4-(7-indolylamino)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,

4-(7-indolylamino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,

4-(7-indolylamino)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,

4-(3-chloroindol-7-ylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,

4-(7-indolylamino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline,

7-(2-acetoxy-3-pyrrolidin-1-ylpropoxy)-4-(3-chloroindol-7-ylamino)-6-methoxyquinazoline,

7-[2-acetoxy-3-(N-isopropyl-N-methylamino)propoxy]-4-(3-chloroindol-7-ylamino)-6-methoxyquinazoline,

7-[2-acetoxy-3-(4-cyanomethylpiperazin-1-yl)propoxy]-4-(3-chloroindol-7-ylamino)-6-methoxyquinazoline,

7-(2-acetoxy-3-piperidinopropoxy)-4-(3-chloroindol-7-ylamino)-6-methoxyquinazoline,

7-(2-acetoxy-3-morpholinopropoxy)-4-(3-chloroindol-7-ylamino)-6-methoxyquinazoline,

4-(3-chloroindol-7-ylamino)-7-(2-hydroxy-3-pyrrolidin-1-ylpropoxy)-6-methoxyquinazoline,

4-(3-chloroindol-7-ylamino)-7-[2-hydroxy-3-(N-isopropyl-N-methylamino)propoxy]-6-methoxyquinazoline,

4-(3-chloroindol-7-ylamino)-7-[3-(4-cyanomethylpiperazin-1-yl)-2-hydroxypropoxy]-6-methoxyquinazoline,

4-(3-chloroindol-7-ylamino)-7-(2-hydroxy-3-piperidinopropoxy)-6-methoxyquinazoline and

4-(3-chloroindol-7-ylamino)-7-(2-hydroxy-3-morpholinopropoxy)-6-methoxyquinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

Further particular Src inhibitors include the following compounds from International Patent Application WO 02/085895 :-

6-methoxy-4-(2,3-methylenedioxyphenoxy)-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,
4-(6-chloro-2,3-methylenedioxyphenoxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,
4-(6-bromo-2,3-methylenedioxyphenoxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,
6-methoxy-4-(2,3-methylenedioxyphenoxy)-7-(3-morpholinopropoxy)quinazoline,
4-(6-chloro-2,3-methylenedioxyphenoxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
4-(6-bromo-2,3-methylenedioxyphenoxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
6-methoxy-4-(2,3-methylenedioxyphenoxy)-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,
4-(6-chloro-2,3-methylenedioxyphenoxy)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,
4-(6-bromo-2,3-methylenedioxyphenoxy)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,
6-methoxy-4-(2,3-methylenedioxyphenoxy)-7-(3-methylsulphonylpropoxy)quinazoline,
4-(6-chloro-2,3-methylenedioxyphenoxy)-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline and
4-(6-bromo-2,3-methylenedioxyphenoxy)-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline;
or a pharmaceutically-acceptable acid-addition salt thereof.

Further particular Src inhibitors include the following compounds from International Patent Application PCT/GB 02/02117 :-

4-(2-chloro-5-methoxyanilino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline,
4-(2-chloro-5-methoxyanilino)-6-methoxy-7-piperidin-4-ylmethoxyquinazoline and
4-(2-bromo-5-methoxyanilino)-6-methoxy-7-[2-(N-methylpiperidin-4-yl)ethoxy]quinazoline;
or a pharmaceutically-acceptable acid-addition salt thereof.

Further particular Src inhibitors include the following compounds from International Patent Application PCT/GB 02/02124 :-

4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline,
4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-piperidin-4-ylmethoxyquinazoline,
4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-[2-(N-methylpiperidin-4-yl)ethoxy]quinazoline and

4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-(2-piperidin-4-ylethoxy)quinazoline;
or a pharmaceutically-acceptable acid-addition salt thereof.

Further particular Src inhibitors include the following compounds from International Patent Application PCT/GB 02/02128 :-

4-(2-chloro-5-methoxyanilino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,
4-(2-chloro-5-methoxyanilino)-6-methoxy-7-(2-piperidinoethoxy)quinazoline and
4-(2-chloro-5-methoxyanilino)-6-methoxy-7-(2-morpholinoethoxy)quinazoline and
4-(2-bromo-5-methoxyanilino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline
or a pharmaceutically-acceptable acid-addition salt thereof.

Further particular Src inhibitors include the following compounds from International Patent Application PCT/GB 02/03177 :-

4-(6-chloro-2,3-methylenedioxyanilino)-3-cyano-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline,
4-(6-chloro-2,3-methylenedioxyanilino)-7-(3-chloropropoxy)-3-cyano-6-methoxyquinoline,
4-(6-chloro-2,3-methylenedioxyanilino)-3-cyano-7-methoxy-5-(N-methylpiperidin-4-yloxy)quinoline,
4-(6-chloro-2,3-methylenedioxyanilino)-3-cyano-7-(2-pyrrolidin-1-ylethoxy)-5-tetrahydropyran-4-yloxyquinoline,
4-(6-chloro-2,3-methylenedioxyanilino)-3-cyano-7-(3-pyrrolidin-1-ylpropoxy)-5-tetrahydropyran-4-yloxyquinoline,
4-(6-chloro-2,3-methylenedioxyanilino)-3-cyano-7-[3-(4-methylpiperazin-1-yl)propoxy]-5-tetrahydropyran-4-yloxyquinoline,
4-(6-chloro-2,3-methylenedioxyanilino)-3-cyano-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinoline,
4-(6-chloro-2,3-methylenedioxyanilino)-3-cyano-7-(2-piperidinoethoxy)-5-tetrahydropyran-4-yloxyquinoline and
4-(6-chloro-2,3-methylenedioxyanilino)-3-cyano-7-(N-methylpiperidin-4-ylmethoxy)-5-tetrahydropyran-4-yloxyquinoline;
or a pharmaceutically-acceptable acid-addition salt thereof.

More particular Src inhibitors include the following compounds :-

4-(2,4-dichloro-5-methoxyanilino)-7-(2-piperidinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(2,4-dichloro-5-methoxyanilino)-7-(2-morpholinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(2,4-dichloro-5-methoxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline,

4-(2-bromo-5-methoxyanilino)-7-(2-pyrrolidin-1-ylethoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-(2-pyrrolidin-1-ylethoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-(3-pyrrolidin-1-ylpropoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-[3-(4-methylpiperazin-1-yl)propoxy]-5-tetrahydropyran-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-(2-piperidinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-morpholinopropoxy)quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-[3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy]quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-piperidinopropoxy)quinazoline,

4-(2-chloro-5-methoxyanilino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline,

4-(2-chloro-5-methoxyanilino)-6-methoxy-7-piperidin-4-ylmethoxyquinazoline,

4-(2-bromo-5-methoxyanilino)-6-methoxy-7-[2-(N-methylpiperidin-4-yl)ethoxy]quinazoline,

4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline,

4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-piperidin-4-ylmethoxyquinazoline and

4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-[2-(N-methylpiperidin-4-yl)ethoxy]quinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

Preferred Src inhibitors include the following compounds :-

4-(2,4-dichloro-5-methoxyanilino)-7-(2-piperidinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(2,4-dichloro-5-methoxyanilino)-7-(2-morpholinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-(2-pyrrolidin-1-ylethoxy)-5-tetrahydropyran-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline,

4-(6-chloro-2,3-methylenedioxyanilino)-7-(2-piperidinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-morpholinopropoxy)quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,

6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-piperidinopropoxy)quinazoline,

4-(2-chloro-5-methoxyanilino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline,

4-(2-chloro-5-methoxyanilino)-6-methoxy-7-piperidin-4-ylmethoxyquinazoline,

4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline and

4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-piperidin-4-ylmethoxyquinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

A particular preferred Src inhibitor for use in the combination of the invention is :-

4-(6-chloro-2,3-methylenedioxyanilino)-7-(2-pyrrolidin-1-ylethoxy)-5-tetrahydropyran-4-yloxyquinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular preferred Src inhibitor for use in the combination of the invention is :-

4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular preferred Src inhibitor for use in the combination of the invention is :-

4-(6-chloro-2,3-methylenedioxyanilino)-7-(2-piperidinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular preferred Src inhibitor for use in the combination of the invention is :-

6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-morpholinopropoxy)quinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular preferred Src inhibitor for use in the combination of the invention is :-

4-(2-chloro-5-methoxyanilino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

A suitable pharmaceutically-acceptable salt of a Src inhibitor that is sufficiently basic is, for example, a pharmaceutically-acceptable acid-addition salt, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, trifluoroacetic, citric or maleic acid. A suitable pharmaceutically-acceptable salt of a Src inhibitor that is sufficiently acidic is, for example, a pharmaceutically-acceptable alkali or alkaline earth metal salt such as a calcium or magnesium salt, or an ammonium salt, or a salt with an organic base such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Gemcitabine (Gemzar, trademark of Lilly Inc.) is the β-isomer of 2'-deoxy-2',2'-difluorocytidine monohydrochloride which has become a useful cytotoxic agent. It is a member of the antimetabolite class of cytotoxic agents.

As stated hereinbefore, the combination of the present invention comprising a Src inhibitor and gemcitabine is useful in the synergistic treatment or prophylaxis of cancer.

Cancers that are amenable to treatment with the combination of the present invention include oesophageal cancer, myeloma, hepatocellular, pancreatic and cervical cancer, Ewings tumour, neuroblastoma, kaposis sarcoma, ovarian cancer, breast cancer, colorectal cancer, prostate cancer, bladder cancer, melanoma, lung cancer [including non small cell lung cancer (NSCLC) and small cell lung cancer (SCLC)], gastric cancer, head and neck cancer, brain cancer, renal cancer, lymphoma and leukaemia. More particularly, the combination of the present invention is useful in the treatment or prevention of pancreatic cancer.

The cancer treatment of the present invention includes an anti-tumour effect that may be assessed by conventional means such as the response rate, the time to disease progression and/or the survival rate. Anti-tumour effects of the present invention include, but are not limited to, inhibition of tumour growth, tumour growth delay, regression of tumour, shrinkage

of tumour, increased time to regrowth of tumour on cessation of treatment and slowing of disease progression. For example, it is expected that when the combination of the present invention is administered to a warm-blooded animal such as a human, in need of treatment for cancer involving a solid tumour, such a method of treatment will produce an effect, as measured by, for example, one or more of: the extent of the anti-tumour effect, the response rate, the time to disease progression and the survival rate.

As described hereinbefore, the combination of the present invention is useful in the synergistic treatment or prophylaxis of cancer. According to the present invention, a combination treatment is defined as affording a synergistic effect if the effect is therapeutically superior, as measured by, for example, the extent of the response, the response rate, the time to disease progression or the survival period, to that achievable on dosing one or other of the components of the combination treatment at its conventional dose. For example, the effect of the combination treatment is synergistic if the effect is therapeutically superior to the effect achievable with a Src inhibitor or gemcitabine alone. Further, the effect of the combination treatment is synergistic if a beneficial effect is obtained in a group of patients that does not respond (or responds poorly) to a Src inhibitor or gemcitabine alone. In addition, the effect of the combination treatment is defined as affording a synergistic effect if one of the components is dosed at its conventional dose and the other component is dosed at a reduced dose and the therapeutic effect, as measured by, for example, the extent of the response, the response rate, the time to disease progression or the survival period, is equivalent to that achievable on dosing conventional amounts of either one of the components of the combination treatment. In particular, synergy is deemed to be present if the conventional dose of the Src inhibitor or gemcitabine may be reduced without detriment to one or more of the extent of the response, the response rate, the time to disease progression and survival data, in particular without detriment to the duration of the response, but with fewer and/or less troublesome side-effects than those that occur when conventional doses of each component are used.

According to a particular aspect of the present invention there is provided a combination comprising a Src inhibitor as defined hereinbefore and gemcitabine for use in the synergistic treatment or prophylaxis of pancreatic cancer.

According to a further particular aspect of the present invention there is provided a combination comprising the Src inhibitor 4-(6-chloro-2,3-methylenedioxyanilino)-7-(2-pyrrolidin-1-ylethoxy)-5-tetrahydropyran-4-yloxyquinazoline, or a pharmaceutically-

acceptable acid-addition salt thereof, and gemcitabine for use in the synergistic treatment or prophylaxis of pancreatic cancer.

According to a further particular aspect of the present invention there is provided a combination comprising the Src inhibitor 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline, or a pharmaceutically-acceptable acid-addition salt thereof, and gemcitabine for use in the synergistic treatment or prophylaxis of pancreatic cancer.

According to a further particular aspect of the present invention there is provided a combination comprising the Src inhibitor 4-(6-chloro-2,3-methylenedioxyanilino)-7-(2-piperidinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline, or a pharmaceutically-acceptable acid-addition salt thereof, and gemcitabine for use in the synergistic treatment or prophylaxis of pancreatic cancer.

According to a further particular aspect of the present invention there is provided a combination comprising the Src inhibitor 6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-morpholinopropoxy)quinazoline, or a pharmaceutically-acceptable acid-addition salt thereof, and gemcitabine for use in the synergistic treatment or prophylaxis of pancreatic cancer.

According to a further particular aspect of the present invention there is provided a combination comprising the Src inhibitor 4-(2-chloro-5-methoxyanilino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline, or a pharmaceutically-acceptable acid-addition salt thereof, and gemcitabine for use in the synergistic treatment or prophylaxis of pancreatic cancer.

The therapeutic combination of the present invention may be administered in the form of a suitable pharmaceutical composition. According to this aspect of the invention there is provided a pharmaceutical composition for use in the synergistic treatment or prophylaxis of cancer which comprises a combination as defined hereinbefore in association with a pharmaceutically-acceptable excipient or carrier.

The compositions described herein may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) for example as a sterile solution, suspension or emulsion, for topical administration for example as an ointment or cream, for rectal administration for example as a suppository or the route of administration may be by direct injection into the tumour or by regional delivery or by local delivery. In

other embodiments of the present invention the Src inhibitor of the combination treatment may be delivered endoscopically, intratracheally, intralesionally, percutaneously, intravenously, subcutaneously, intraperitoneally or intratumourally. In general the compositions described herein may be prepared in a conventional manner using conventional excipients or carriers that are well known in the art.

Suitable pharmaceutically-acceptable excipients or carriers for a tablet formulation include, for example, inert excipients such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or alginic acid; binding agents such as gelatin or starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl 4-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid excipient, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

The compositions of the present invention are advantageously presented in unit dosage form. A Src inhibitor as defined hereinbefore will generally be administered so that a daily dose in the range, for example, 0.1 mg/kg to 75 mg/kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.1 mg/kg to 30 mg/kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.05 mg/kg to 25 mg/kg body weight will be used. Oral administration is however preferred, particularly in tablet form. Typically, unit dosage forms will contain about 0.5 mg to 0.5 g of the Src inhibitor.

Gemcitabine may be administered according to known clinical practice. For example, in NSCLC the recommended dose of gemcitabine is 1000mg/m^2 given by 30 minute intravenous infusion. This may be repeated once weekly for three weeks, followed by a one week rest period. This four week cycle may then be repeated. Dosage reduction may be necessary if the patient experiences undue toxicity. In pancreatic cancer the recommended

dose of gemcitabine is 1000mg/m^2 given by 30 minute intravenous infusion. This may be repeated once weekly for seven weeks followed by a week of rest. Subsequent cycles may consist of injections once weekly for three consecutive weeks out of every four weeks. Dosage reduction may be necessary if the patient experiences undue toxicity.

The dosages and schedules described hereinbefore may be varied according to the particular disease state and the overall condition of the patient. For example, it may be necessary or desirable to reduce the above-mentioned doses of the components of the combination treatment in order to reduce toxicity. Dosages and schedules may also vary if, in addition to a combination treatment of the present invention, one or more additional chemotherapeutic agents are used. Scheduling can be determined by the practitioner who is treating any particular patient using his professional skill and knowledge.

It will be appreciated that the pharmaceutical composition according to the present invention includes a composition comprising a Src inhibitor as defined hereinbefore and gemcitabine and a pharmaceutically-acceptable excipient or carrier. Such a composition conveniently provides the therapeutic combination product of the invention for simultaneous administration in the synergistic treatment or prophylaxis of cancer.

A pharmaceutical composition according to the present invention also includes separate compositions comprising a first composition comprising a Src inhibitor and a pharmaceutically-acceptable excipient or carrier, and a second composition comprising gemcitabine and a pharmaceutically-acceptable excipient or carrier. Such a composition conveniently provides the therapeutic combination of the invention for sequential or separate administration in the synergistic treatment or prophylaxis of cancer but the separate compositions may also be administered simultaneously.

Conveniently such a pharmaceutical composition of the invention comprises a kit comprising a first container with a suitable composition containing the Src inhibitor and a second container with a suitable composition containing gemcitabine. According to this aspect of the present invention there is provided a kit for use in the synergistic treatment or prophylaxis of cancer comprising :-

a) a Src inhibitor together with a pharmaceutically-acceptable excipient or carrier, in a first unit dosage form;

b) gemcitabine together with a pharmaceutically-acceptable excipient or carrier, in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to this aspect of the invention there is also provided a pharmaceutical composition for use in the synergistic treatment or prophylaxis of pancreatic cancer which comprises a combination as defined hereinbefore in association with a pharmaceutically-acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a combination as defined hereinbefore for use in the synergistic treatment or prophylaxis of cancer.

According to this aspect of the present invention there is also provided a combination as defined hereinbefore for use in the synergistic treatment or prophylaxis of pancreatic cancer.

According to a further aspect of the present invention there is provided the use of a combination as defined hereinbefore in the manufacture of a medicament for administration to a warm-blooded animal such as man to provide the synergistic treatment or prophylaxis of cancer.

According to this aspect of the present invention there is also provided the use of a combination as defined hereinbefore in the manufacture of a medicament for administration to a warm-blooded animal such as man to provide the synergistic treatment or prophylaxis of pancreatic cancer.

According to a further aspect of the present invention there is provided a method for the synergistic treatment or prophylaxis of cancer which comprises the administration to a warm-blooded animal such as man that is in need of such treatment of effective amounts of the components of the combination as defined hereinbefore.

According to this aspect of the present invention there is also provided a method for the synergistic treatment or prophylaxis of pancreatic cancer which comprises the administration to a warm-blooded animal such as man that is in need of such treatment of effective amounts of the components of the combination as defined hereinbefore.

According to this aspect of the present invention there is also provided a method for the synergistic treatment or prophylaxis of cancer which comprises the administration to a warm-blooded animal such as man that is in need of such treatment of an effective amount of a Src inhibitor as defined hereinbefore before, simultaneously with or after the administration of an effective amount of gemcitabine.

According to this aspect of the present invention there is also provided a method for the synergistic treatment or prophylaxis of cancer which comprises the simultaneous, sequential or separate administration to a warm-blooded animal such as man that is in need of

such treatment of effective amounts of the components of the combination as defined hereinbefore.

According to this aspect of the present invention there is also provided a method for the synergistic treatment or prophylaxis of pancreatic cancer which comprises the simultaneous, sequential or separate administration to a warm-blooded animal such as man that is in need of such treatment of effective amounts of the components of the combination as defined hereinbefore.

According to this aspect of the present invention there is also provided a method for the synergistic treatment or prophylaxis of cancer which comprises the administration to a warm-blooded animal such as man that is in need of such treatment of an effective amount of a Src inhibitor as defined hereinbefore and the simultaneous, sequential or separate administration of an effective amount of gemcitabine.

According to this aspect of the present invention there is also provided a method for the synergistic treatment or prophylaxis of pancreatic cancer which comprises the administration to a warm-blooded animal such as man that is in need of such treatment of an effective amount of a Src inhibitor as defined hereinbefore and the simultaneous, sequential or separate administration of an effective amount of gemcitabine.

A combination treatment of the present invention as defined hereinbefore may be administered as a sole therapy or may in addition involve surgery or radiotherapy or the administration of an additional chemotherapeutic agent.

Surgery may comprise the step of partial or complete tumour resection, prior to, during or after the administration of the combination treatment of the present invention.

Other chemotherapeutic agents for optional use with the combination treatment of the present invention may include, for example, the following four categories of therapeutic agent :-

(i) antiproliferative/antineoplastic drugs and combinations thereof as used in medical oncology (for example carboplatin and cisplatin);

(ii) cytostatic agents;

(iii) biological response modifiers (for example interferon); and

(iv) antibodies (for example edrecolomab).

For example, the administration of a triple combination of a Src inhibitor as defined hereinbefore, gemcitabine and ionising radiation may produce anti-cancer effects, such as

anti-tumour effects, that are greater than those achieved by the administration of any two components of the triple combination.

According to this aspect of the present invention there is provided a method for the synergistic treatment or prophylaxis of cancer which comprises the administration to a warm-blooded animal such as man that is in need of such treatment of an effective amount of a Src inhibitor as defined hereinbefore before, simultaneously with or after an effective amount of gemcitabine and before, simultaneously with or after an effective amount of ionising radiation.

According to this aspect of the present invention there is also provided a method for the synergistic treatment or prophylaxis of pancreatic cancer which comprises the administration to a warm-blooded animal such as man that is in need of such treatment of an effective amount of a Src inhibitor as defined hereinbefore before, simultaneously with or after an effective amount of gemcitabine and before, simultaneously with or after an effective amount of ionising radiation.

The ionising radiation may be given to said warm-blooded animal such as man within the period of a week before to a week after the administration of the combination of the present invention as defined hereinbefore.

Radiotherapy may be administered according to the known practices in clinical radiotherapy. The dosages of ionising radiation will be those known for use in clinical radiotherapy. The radiation therapy used will include for example the use of γ-rays, X-rays, and/or the directed delivery of radiation from radioisotopes. Other forms of DNA damaging factors are also included in the present invention such as microwaves and UV-irradiation. For example X-rays may be dosed in daily doses of 1.8-2.0Gy, 5 days a week for 5-6 weeks. Normally a total fractionated dose will lie in the range 45-60Gy. Single larger doses, for example 5-10Gy may be administered as part of a course of radiotherapy. Single doses may be administered intraoperatively. Hyperfractionated radiotherapy may be used whereby small doses of X-rays are administered regularly over a period of time, for example 0.1Gy per hour over a number of days. Dosage ranges for radioisotopes vary widely, and depend on the half-life of the isotope, the strength and type of radiation emitted, and on the uptake by cells.

According to a further aspect of the present invention there is provided the use of a combination as defined hereinbefore in the manufacture of a medicament for administration to

a warm-blooded animal such as man that is being treated with ionising radiation to provide the synergistic treatment or prophylaxis of cancer.

The following test method may be used to demonstrate the activity of the Src inhibitor 4-(2-chloro-5-methoxyanilino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline (hereinafter identified by way of the code number Src 1) when administered in combination with gemcitabine.

The test method has been described by C J Bruns *et al.*, Cancer Research, 2000, 60, 2926-2935 and involves the injection of pancreatic tumour cells derived from the COLO 357 human pancreatic cancer cell line into pancreas tissue in a group of nude mice and an evaluation of tumour growth and metastasis into liver node tissue.

L3.6pl pancreatic cancer cells were obtained after successive cycles of cell selection from nude mouse tumour tissue that developed after injection of COLO 357 human pancreatic cancer cells. L3.6pl cancer cells ($1x10^6$ cells) were injected into the pancreas of each animal in several groups of male athymic nude mice (n = 8 to 10 per group). After a period of 9 days, groups of test animals were treated with the test compound Src-1 (50 mg/kg or 25 mg/kg orally by gavage daily for 5 days per week on treatment days 1-5 and 8-12), with gemcitabine (100 mg/kg by intraperitoneal injection twice weekly on treatment days 2, 5, 9 and 12) or with a combination of both agents (*i.e.* gemcitabine by intraperitoneal injection twice weekly at 100 mg/kg on treatment days 2, 5, 9 and 12 and Src-1 at 50 mg/kg orally by gavage daily on treatment days 1-5 and 8-12).

On the days where both agents were given, the gemcitabine was dosed at least 1 hour before test compound Src-1. A control group of 10 mice received intraperitoneal injections of an equivalent volume of saline according to the same treatment schedule as the combination group. The animals were sacrificed 32 days after tumour cell injection. The pancreatic tumour weight was measured. The incidence of liver metastases was evaluated. All macroscopically enlarged liver nodules were evaluated by histopathology to confirm tumour metastasis.

The results are shown in the table which follows :-

Treatment Group	Liver Metastases	Average Tumour Weight (mg) +/- std dev	Average Body Weight (g) +/- std dev
Control	3/5	1359 +/- 397	24.2 +/- 1.9
gemcitabine	1/5	393 +/- 68	22.7 +/- 1.5
Src-1 (50 mg/kg)	0/9	827 +/- 176	22.3 +/- 6.8
Src-1 (25 mg/kg)	0/9	816 +/- 118	22.6 +/- 1.4
Src-1 (50 mg/kg) + gemcitabine	0/8	124 +/- 92	18.3 +/- 1.7

Abbreviation std dev = standard deviation

The results demonstrate that, compared with the weight of control tumours, tumour growth in those animals treated with the combination of Src-1 (50 mg/kg) plus gemcitabine was much reduced (1359 mg and 124 mg respectively) to a level well below that achievableon the dosing of either gemcitabine of the Src inhibitor alone . In addition, there was no liver metastasis in the animals treated with the combination of Src-1 (50 mg/kg) plus gemcitabine whereas liver metastasis was present in 1/5 of the animals treated with gemcitabine alone.

Src Inhibitors described within International Patent Application PCT/GB 02/02117

Example 1 **4-(2-chloro-5-methoxyanilino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline**

A mixture of 4-chloro-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline (0.18 g), 2-chloro-5-methoxyaniline (0.188 g), a 6.2M solution of hydrogen chloride in isopropanol (0.15 ml) and isopropanol (4 ml) was stirred and heated to 80°C for 2.5 hours. The mixture was cooled to ambient temperature and evaporated. The residue was triturated under diethyl ether. The solid so obtained was isolated, washed in turn with isopropanol and diethyl ether and dried under vacuum. The material so obtained was dissolved in methylene chloride and a saturated methanolic ammonia solution (0.5 ml) was added and the mixture was stirred at ambient temperature for 10 minutes. The resultant mixture was filtered, the filtrate was evaporated and the residue was purified by column chromatography on silica using a 19:1 mixture of methylene chloride and a saturated methanolic ammonia solution as eluent. The material so obtained was triturated under diethyl ether and the solid so obtained

was isolated, washed with diethyl ether and dried under vacuum. There was thus obtained the title compound (0.07 g); NMR Spectrum: ($DMSOd_6$) 1.3-1.4 (m, 2H), 1.78 (m, 3H), 1.9 (m, 2H), 2.15 (s, 3H), 2.8 (d, 2H), 3.8 (s, 3H), 3.95 (s, 3H), 4.0 (d, 2H), 6.9 (d, 1H), 7.15 (m, 2H), 7.48 (d, 1H), 7.8 (s, 1H), 8.3 (s, 1H), 9.5 (br s, 1H); Mass Spectrum: $M+H^+$ 443 and 445.

The 4-chloro-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline used as a starting material was prepared as follows :-

A solution of di-tert-butyl dicarbonate (41.7 g) in ethyl acetate (75 ml) was added dropwise to a stirred solution of ethyl piperidine-4-carboxylate (30 g) in ethyl acetate (150 ml) which had been cooled to 0 to 5°C in an ice-bath. The resultant mixture was stirred at ambient temperature for 48 hours. The mixture was poured into water (300 ml). The organic layer was separated, washed in turn with water (200 ml), 0.1N aqueous hydrochloric acid solution (200 ml), a saturated aqueous sodium bicarbonate solution (200 ml) and brine (200 ml), dried over magnesium sulphate and evaporated. There was thus obtained ethyl N-tert-butoxycarbonylpiperidine-4-carboxylate (48 g); NMR Spectrum: ($CDCl_3$) 1.25 (t, 3H), 1.45 (s, 9H), 1.55-1.7 (m, 2H), 1.8-2.0 (d, 2H), 2.35-2.5 (m, 1H), 2.7-2.95 (t, 2H), 3.9-4.1 (br s, 2H), 4.15 (q, 2H).

A solution of the material so obtained in THF (180 ml) was cooled at 0°C and lithium aluminium hydride (1M solution in THF; 133 ml) was added dropwise. The mixture was stirred at 0°C for 2 hours. Water (30 ml) and 2N aqueous sodium hydroxide solution (10 ml) were added in turn and the mixture was stirred for 15 minutes. The resultant mixture was filtered through diatomaceous earth and the solids were washed with ethyl acetate. The filtrate was washed in turn with water and with brine, dried over magnesium sulphate and evaporated. There was thus obtained N-tert-butoxycarbonyl-4-hydroxymethylpiperidine (36.3 g); NMR Spectrum: ($CDCl_3$) 1.05-1.2 (m, 2H), 1.35-1.55 (m, 10H), 1.6-1.8 (m, 2H), 2.6-2.8 (t, 2H), 3.4-3.6 (t, 2H), 4.0-4.2 (br s, 2H).

1,4-Diazabicyclo[2.2.2]octane (42.4 g) was added to a solution of N-tert-butoxycarbonyl-4-hydroxymethylpiperidine (52.5 g) in tert-butyl methyl ether (525 ml) and the mixture was stirred at ambient temperature for 15 minutes. The mixture was then cooled in an ice-bath to 5°C and a solution of 4-toluenesulphonyl chloride (62.8 g) in tert-butyl methyl ether (525 ml) was added dropwise over 2 hours while maintaining the reaction temperature at approximately 0°C. The resultant mixture was allowed to warm to ambient temperature and was stirred for 1 hour. Petroleum ether (b.p. 60-80°C, 1L) was added and the precipitate was removed by filtration. The filtrate was evaporated to give a

solid residue which was dissolved in diethyl ether. The organic solution was washed in turn with 0.5N aqueous hydrochloric acid solution, water, a saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and evaporated. There was thus obtained N-tert-butoxycarbonyl-4-(4-toluenesulphonyloxymethyl)piperidine (76.7 g); NMR Spectrum: ($CDCl_3$) 1.0-1.2 (m, 2H), 1.45 (s, 9H), 1.65 (d, 2H), 1.75-1.9 (m, 2H), 2.45 (s, 3H), 2.55-2.75 (m, 2H), 3.85 (d, 1H), 4.0-4.2 (br s, 2H), 7.35 (d, 2H), 7.8 (d, 2H).

A portion (40 g) of the material so obtained was added to a suspension of ethyl 4-hydroxy-3-methoxybenzoate (19.6 g) and potassium carbonate (28 g) in DMF (200 ml) and the resultant mixture was stirred and heated to 95°C for 2.5 hours. The mixture was cooled to ambient temperature and partitioned between water and a mixture of ethyl acetate and diethyl ether. The organic layer was washed in turn with water and brine, dried over magnesium sulphate and evaporated. The resulting oil was crystallised from petroleum ether (b.p. 60-80°C) and the suspension was stored overnight at 5°C. The resultant solid was collected by filtration, washed with petroleum ether and dried under vacuum. There was thus obtained ethyl 4-(N-tert-butoxycarbonylpiperidin-4-ylmethoxy)-3-methoxybenzoate (35 g); m.p. 81-83°C; NMR Spectrum: ($CDCl_3$) 1.2-1.35 (m, 2H), 1.4 (t, 3H), 1.48 (s, 9H), 1.8-1.9 (d, 2H), 2.0-2.15 (m, 2H), 2.75 (t, 2H), 3.9 (d, 2H), 3.95 (s, 3H), 4.05-4.25 (br s, 2H), 4.35 (q, 2H), 6.85 (d, 1H), 7.55 (s, 1H), 7.65 (d, 1H).

The material so obtained was dissolved in formic acid (35 ml), formaldehyde (12M, 37% in water, 35 ml) was added and the mixture was stirred and heated to 95°C for 3 hours. The resultant mixture was evaporated. The residue was dissolved in methylene chloride and hydrogen chloride (3M solution in diethyl ether; 40 ml) was added. The mixture was diluted with diethyl ether and the mixture was triturated until a solid was formed. The solid was collected, washed with diethyl ether and dried under vacuum overnight at 50°C. There was thus obtained ethyl 3-methoxy-4-(N-methylpiperidin-4-ylmethoxy)benzoate (30.6 g); NMR Spectrum: ($DMSOd_6$) 1.29 (t, 3H), 1.5-1.7 (m, 2H), 1.95 (d, 2H), 2.0-2.15 (br s, 1H), 2.72 (s, 3H), 2.9-3.1 (m, 2H), 3.35-3.5 (br s, 2H), 3.85 (s, 3H), 3.9-4.05 (br s, 2H), 4.3 (q, 2H), 7.1 (d, 1H), 7.48 (s, 1H), 7.6 (d, 1H).

The material so obtained was dissolved in methylene chloride (75 ml) and the solution was cooled in an ice-bath to 0-5°C. Trifluoroacetic acid (37.5 ml) was added followed by the dropwise addition over 15 minutes of a solution of fuming nitric acid (24M; 7.42 ml) in methylene chloride (15 ml). The resultant solution was allowed to warm to ambient temperature and was stirred for 2 hours. Volatile materials were evaporated. The residue was

dissolved in methylene chloride (50 ml) and the solution was cooled in an ice-bath to 0-5°C. Diethyl ether was added and the resultant precipitate was collected and dried under vacuum at 50°C. The solid was dissolved in methylene chloride (500 ml) and hydrogen chloride (3M solution in diethyl ether; 30 ml) was added followed by diethyl ether (500 ml). The resultant solid was collected and dried under vacuum at 50°C. There was thus obtained ethyl 5-methoxy-4-(N-methylpiperidin-4-ylmethoxy)-2-nitrobenzoate (28.4 g); NMR Spectrum: ($DMSOd_6$) 1.3 (t, 3H), 1.45-1.65 (m, 2H), 1.75-2.1 (m, 3H), 2.75 (s, 3H), 2.9-3.05 (m, 2H), 3.4-3.5 (d, 2H), 3.95 (s, 3H), 4.05 (d, 2H), 4.3 (q, 2H), 7.32 (s, 1H), 7.66 (s, 1H).

A mixture of a portion (3.89 g) of the material so obtained, 10% platinum-on-activated carbon (50% wet, 0.389 g) and methanol (80 ml) was stirred under 1.8 atmospheres pressure of hydrogen until uptake of hydrogen ceased. The mixture was filtered and the filtrate was evaporated. The residue was dissolved in water (30 ml) and basified to pH10 by the addition of a saturated aqueous sodium bicarbonate solution. The mixture was diluted with a 1:1 mixture of ethyl acetate and diethyl ether and the organic layer was separated. The aqueous layer was further extracted with a 1:1 mixture of ethyl acetate and diethyl ether and the organic extracts were combined, washed in turn with water and brine, dried over magnesium sulphate and evaporated. The residue was triturated under a mixture of petroleum ether (b.p. 60-80°C) and diethyl ether. The solid so obtained was isolated, washed with petroleum ether and dried under vacuum at 60°C. There was thus obtained ethyl 2-amino-5-methoxy-4-(N-methylpiperidin-4-ylmethoxy)benzoate (2.58 g); m.p. 111-112°C; NMR Spectrum: ($CDCl_3$) 1.35 (t, 3H), 1.4-1.5 (m, 2H), 1.85 (m, 3H), 1.95 (t, 2H), 2.29 (s, 3H), 2.9 (d, 2H), 3.8 (s, 3H), 3.85 (d, 2H), 4.3 (q, 2H), 5.55 (br s, 2H), 6.13 (s, 1H), 7.33 (s, 1H).

A mixture of ethyl 2-amino-5-methoxy-4-(N-methylpiperidin-4-ylmethoxy)benzoate (16.1 g), formamidine acetic acid salt (5.2 g) and 2-methoxyethanol (160 ml) was stirred and heated at 115°C for 2 hours. Further formamidine acetic acid salt (10.4 g) was added in portions every 30 minutes during 4 hours and heating was continued for 30 minutes after the last addition. The resultant mixture was evaporated. The solid residue was stirred under a mixture of methylene chloride (50ml) and ethanol (100ml). The precipitate was removed by filtration and the filtrate was concentrated to a final volume of 100ml. The resultant suspension was cooled to 5°C. The solid so obtained was collected, washed with cold ethanol and with diethyl ether and dried under vacuum at 60°C. There was thus obtained 6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)-3,4-dihydroquinazolin-4-one (12.7 g); NMR Spectrum:

($DMSOd_6$) 1.25-1.4 (m, 2H), 1.75 (d, 2H), 1.9 (t, 1H), 1.9 (s, 3H), 2.16 (s, 2H), 2.8 (d, 2H), 3.9 (s, 3H), 4.0 (d, 2H), 7.11 (s, 1H), 7.44 (s, 1H), 7.97 (s, 1H).

A mixture of a portion (2.8 g) of the material so obtained, thionyl chloride (28 ml) and DMF (0.28 ml) was heated to reflux for 1 hour. The mixture was evaporated and the precipitate was triturated under diethyl ether. The resultant solid was isolated and washed with diethyl ether. The solid was then dissolved in methylene chloride and the solution was washed with a saturated aqueous sodium bicarbonate solution. The organic layer was washed in turn with water and brine, dried over magnesium sulphate and evaporated. There was thus obtained 4-chloro-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline (2.9 g), NMR Spectrum: ($DMSOd_6$) 1.3-1.5 (m, 2H), 1.75-1.9 (m, 4H), 2.0 (t, 1H), 2.25 (s, 3H), 2.85 (d, 2H), 4.02 (s, 3H), 4.12 (d, 2H), 7.41 (s, 1H), 7.46 (s, 1H), 8.9 (s, 1H).

Example 2 4-(2-chloro-5-methoxyanilino)-6-methoxy-7-piperidin-4-ylmethoxyquinazoline monohydrochloride salt

A mixture of 4-chloro-6-methoxy-7-(N-tert-butoxycarbonylpiperidin-4-ylmethoxy)quinazoline (0.08 g), 2-chloro-5-methoxyaniline hydrochloride (0.042 g), a 6M solution of hydrogen chloride in isopropanol (0.036 ml) and isopropanol (4 ml) was stirred and heated to 80°C for 1.5 hours. The mixture was cooled to ambient temperature and the precipitate was isolated, washed in turn with isopropanol and diethyl ether and dried under vacuum. There was thus obtained the title compound (0.045 g); NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 1.5-1.65 (m, 2H), 1.98 (d, 2H), 2.15-2.3 (m, 1H), 2.95 (t, 2H), 3.35 (d, 2H), 3.8 (s, 3H), 4.0 (s, 3H), 4.11 (d, 2H), 7.05 (m, 1H), 7.17 (d, 1H), 7.36 (s, 1H), 7.54 (d, 1H), 8.13 (s, 1H), 8.82 (s, 1H); Mass Spectrum: $M-H^-$ 427 and 429.

The 7-(N-tert-butoxycarbonylpiperidin-4-ylmethoxy)-4-chloro-6-methoxyquinazoline used as a starting material was prepared as follows :-

Sodium hydride (60% suspension in mineral oil, 1.44 g) was added portionwise during 20 minutes to a solution of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (International Patent Application WO 97/22596, Example 1 thereof; 8.46 g) in DMF (70 ml). The mixture was stirred at ambient temperature for 1.5 hours. Chloromethyl pivalate (5.65 g) was added dropwise and the mixture was stirred at ambient temperature for 2 hours. The mixture was diluted with ethyl acetate (100 ml) and poured onto a mixture (400 ml) of ice and water containing 2N aqueous hydrochloric acid (4 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined extracts were washed with

brine, dried over magnesium sulphate and evaporated. The residue was triturated under a mixture of diethyl ether and petroleum ether (b.p. 60-80°C) and the resultant solid was collected and dried under vacuum. There was thus obtained 7-benzyloxy-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (10 g); NMR Spectrum: ($DMSOd_6$) 1.11 (s, 9H), 3.89 (s, 3H), 5.3 (s, 2H), 5.9 (s, 2H), 7.27 (s, 1H), 7.35 (m, 1H), 7.47 (t, 2H), 7.49 (d, 2H), 7.51 (s, 1H), 8.34 (s, 1H).

A mixture of a portion (7 g) of the material so obtained, 10% palladium-on-charcoal catalyst (0.7 g), DMF (50 ml), methanol (50 ml), acetic acid (0.7 ml) and ethyl acetate (250 ml) was stirred under an atmosphere pressure of hydrogen for 40 minutes. The catalyst was removed by filtration and the solvent was evaporated. The residue was triturated under diethyl ether and the resultant solid was collected and dried under vacuum. There was thus obtained 7-hydroxy-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (4.36 g); NMR Spectrum: ($DMSOd_6$) 1.1 (s, 9H), 3.89 (s, 3H), 5.89 (s, 2H), 7.0 (s, 1H), 7.48 (s, 1H), 8.5 (s, 1H).

Using an analogous procedure to that described in the fourth paragraph of the portion of Example 1 that is concerned with the preparation of starting materials, 7-hydroxy-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one was reacted with N-tert-butoxycarbonyl-4-(4-toluenesulphonyloxymethyl)piperidine to give 7-(N-tert-butoxycarbonylpiperidin-4-ylmethoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one.

A mixture of 7-(N-tert-butoxycarbonylpiperidin-4-ylmethoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (6 g) and a saturated methanolic ammonia solution (100ml) was stirred at ambient temperature for 16 hours. The resultant mixture was evaporated and the residue was triturated under diethyl ether. The solid so obtained was isolated, washed with a 49:1 mixture of diethyl ether and methylene chloride and dried under vacuum. There was thus obtained 7-(N-tert-butoxycarbonylpiperidin-4-ylmethoxy)-6-methoxy-3,4-dihydroquinazolin-4-one (3.3 g); NMR Spectrum: ($DMSOd_6$) 1.12-1.3 (m, 2H), 1.42 (s, 9H), 1.8 (d, 2H), 2.02 (m, 1H), 2.7-2.9 (m, 2H), 3.9 (s, 3H), 4.02 (d, 4H), 7.15 (s, 1H), 7.45 (s, 1H), 8.0 (s, 1H).

A mixture of a portion (0.2 g) of the material so obtained, carbon tetrachloride (0.15 ml), triphenylphosphine (0.25 g) and 1,2-dichloroethane (10 ml) was stirred and heated to 70°C for 2 hours. The mixture was evaporated and the residue was purified by column chromatography on silica using a 5:4:1 mixture of methylene chloride, ethyl acetate and

methanol as eluent. There was thus obtained 7-(N-tert-butoxycarbonylpiperidin-4-ylmethoxy)-4-chloro-6-methoxyquinazoline (0.07 g); NMR Spectrum: ($DMSOd_6$) 1.15-1.3 (m, 2H), 1.45 (s, 9H), 1.8 (d, 2H), 2.08 (m, 1H), 2.7-2.9 (m, 2H), 4.02 (m, 5H), 4.12 (d, 2H), 7.42 (s, 1H), 7.5 (s, 1H), 8.9 (s, 1H); Mass Spectrum: $M+H^+$ 408.

Example 3 **4-(2-bromo-5-methoxyanilino)-6-methoxy-7-[2-(N-methylpiperidin-4-yl)ethoxy]quinazoline dihydrochloride salt**

A mixture of 4-chloro-6-methoxy-7-[2-(N-methylpiperidin-4-yl)ethoxy]quinazoline (International Patent Application WO 00/47212, example 241; 0.15 g), 2-bromo-5-methoxyaniline (0.113 g), a 6M solution of hydrogen chloride in isopropanol (0.075 ml) and isopropanol (5 ml) was stirred and heated to 80°C for 2 hours. The mixture was cooled to ambient temperature and diethyl ether was added. The resultant solid was isolated, washed with diethyl ether and dried under vacuum. There was thus obtained the title compound (0.12 g); NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 1.5 (m, 2H), 1.8 (m, 3H), 2.0 (m, 2H), 2.75 (s, 3H), 2.95 (t, 2H), 3.4 (m, 2H), 3.8 (s, 3H), 4.0 (s, 3H), 4.3 (m, 2H), 7.0 (m, 1H), 7.2 (d, 1H), 7.45 (s, 1H), 7.7 (d, 1H), 8.2 (s, 1H), 8.85 (s, 1H); Mass Spectrum: $M-H^-$ 499 and 501.

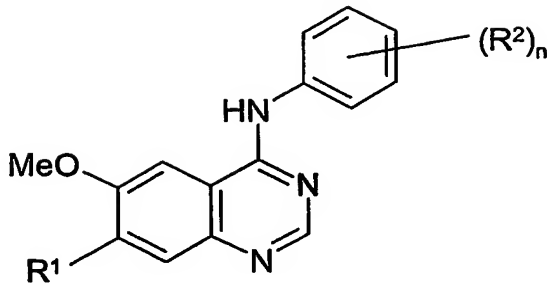
The 2-bromo-5-methoxyaniline used as a starting material was obtained as follows ;-

A mixture of hydrazine hydrate (1 ml), Raney nickel (0.13 g) and methanol was stirred and heated to reflux and a solution of 2-bromo-5-methoxy-1-nitrobenzene (1 g) in methanol (18 ml) was added dropwise. The resultant mixture was heated to reflux for a further 15 minutes. The reaction mixture was cooled to ambient temperature, filtered and evaporated. The residue was partitioned between methylene chloride and water. The organic phase was dried over magnesium sulphate and evaporated to give 2-bromo-5-methoxyaniline (0.8 g); NMR Spectrum: ($DMSOd_6$) 3.65 (s, 3H), 5.25 (br s, 2H), 6.1 (m, 1H), 6.4 (d, 1H), 7.2 (d, 1H).

Example 4

Using an analogous procedure to that described in Example 2 or Example 3, the appropriate 4-chloroquinazoline was reacted with the appropriate aniline to give the compounds described in Table I. Unless otherwise stated, each compound described in Table I was obtained as a dihydrochloride salt.

Table I



Compound No. & Note	R^1	$(R^2)_n$
[1]	3-pyrrolidin-1-ylpropoxy	2-chloro-5-methoxy
[2]	3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy	2-chloro-5-methoxy
[3]	2-(N-methylpiperidin-4-yl)ethoxy	2-chloro-5-methoxy
[4]	2-piperidin-4-ylethoxy	2-bromo-5-methoxy
[5]	piperidin-4-ylmethoxy	2-bromo-5-methoxy
[6]	2-acetoxy-3-piperidinopropoxy	2-bromo-5-methoxy
[7]	2-acetoxy-3-(4-cyanomethylpiperazin-1-yl)propoxy	2-bromo-5-methoxy

Notes

[1] The procedure of Example 3 was followed. The product gave the following characterising data: NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 1.9 (m, 2H), 2.05 (m, 2H), 2.3 (m, 2H), 3.05 (m, 2H), 3.35 (m, 2H), 3.6 (m, 2H), 3.8 (s, 3H), 4.0 (s, 3H), 4.35 (m, 2H), 7.05 (m, 1H), 7.15 (d, 1H), 7.45 (s, 1H), 7.55 (d, 1H), 8.25 (s, 1H), 8.8 (s, 1H); Mass Spectrum: $M+H^+$ 443 and 445.

The 4-chloro-7-(3-pyrrolidin-1-ylpropoxy)-6-methoxyquinazoline used as a starting material was prepared as follows :-

A mixture of 4-hydroxy-3-methoxybenzoic acid (8.4 g), 3-(pyrrolidin-1-yl)propyl chloride (J. Amer. Chem. Soc., 1955, 77, 2272; 14.75 g), potassium carbonate (13.8 g), potassium iodide (1.66 g) and DMF (150 ml) was stirred and heated to 100°C for 3 hours. The mixture was allowed to cool to ambient temperature, filtered and the filtrate was evaporated. The residue was dissolved in ethanol (75 ml), 2N aqueous sodium hydroxide solution (75 ml) was added and the mixture was heated to 90°C for 2 hours. The mixture was concentrated by evaporation and acidified by the addition of concentrated aqueous hydrochloric acid. The resultant mixture was washed with diethyl ether and then purified by

column chromatography using a Diaion (trade mark of Mitsubishi) HP20SS resin column, eluting with water and then with a gradient of methanol (0 to 25%) in dilute hydrochloric acid (pH2.2). The methanol was removed by evaporation and the aqueous residue was freeze dried to give 3-methoxy-4-(3-pyrrolidin-1-ylpropoxy)benzoic acid hydrochloride (12.2 g); NMR Spectrum: (DMSOd_6 and CF_3CO_2D) 2.2 (m, 2H), 3.15 (t, 2H), 3.3 (t, 2H), 3.5 (d, 2H), 3.7 (t, 2H), 3.82 (s, 3H), 4.05 (d, 2H), 4.15 (t, 2H), 7.07 (d, 1H), 7.48 (s, 1H), 7.59 (d, 1H).

The material so obtained was dissolved in trifluoroacetic acid (40 ml) and the solution was cooled to 0°C. Fuming nitric acid (2.4 ml) was added slowly. The cooling bath was removed and the reaction mixture was stirred at ambient temperature for 1 hour. The mixture was evaporated and a mixture of ice and water was added to the residue. The mixture was evaporated. The solid residue was dissolved in dilute hydrochloric acid (pH2.2) and purified by column chromatography using a Diaion HP20SS resin column using a gradient of methanol (0 to 50%) in water. Concentration of the fractions by evaporation gave a precipitate which was collected and dried under vacuum over phosphorus pentoxide. There was thus obtained 5-methoxy-2-nitro-4-(3-pyrrolidin-1-ylpropoxy)benzoic acid hydrochloride (12.1 g, 90%); NMR Spectrum: (DMSOd_6 and CF_3CO_2D) 1.8-1.9 (m, 2H), 2.0-2.1 (m, 2H), 2.1-2.2 (m, 2H), 3.0-3.1 (m, 2H), 3.3 (t, 2H), 3.6-3.7 (m, 2H), 3.95 (s, 3H), 4.25 (t, 2H), 7.35 (s, 1H), 7.62 (s, 1H).

A mixture of a portion (9.63 g) of the material so obtained, thionyl chloride (20 ml) and DMF (0.05 ml) was heated to 45°C for 1.5 hours. The excess thionyl chloride was evaporated using the evaporation of added toluene (x2) to remove the last traces. The resultant solid was suspended in a mixture of THF (250 ml) and methylene chloride (100ml) and ammonia was bubbled though the mixture for 30 minutes. The resultant mixture was stirred for a further 1.5 hours at ambient temperature. The volatiles were removed by evaporation and the residue was dissolved in water and purified by column chromatography using a Diaion HP20SS resin column eluting with a gradient of methanol (0 to 5%) in water. The solvent was removed by evaporation from the fractions containing product. The residue was dissolved in a minimum of methanol and the solution was diluted with diethyl ether. The resultant precipitate was collected by filtration, washed with diethyl ether and dried under vacuum to give 5-methoxy-2-nitro-4-(3-pyrrolidin-1-ylpropoxy)benzamide (7.23 g); NMR Spectrum: (DMSOd_6 and CF_3CO_2D) 1.85-1.95 (m, 2H), 2-2.1 (m, 2H), 2.15-2.25 (m, 2H), 3.0-3.1 (m, 2H), 3.31 (t, 2H), 3.62 (t, 2H), 3.93 (s, 3H), 4.2 (t, 2H), 7.16 (s, 1H), 7.6 (s, 1H).

A mixture of a portion (1.5 g) of the material so obtained, concentrated aqueous hydrochloric acid (5 ml) and methanol (20 ml) was warmed to 50°C to give a solution. Iron powder (1.3 g) was added in portions and the reaction mixture was heated to reflux for 1 hour. The mixture was allowed to cool to ambient temperature. Insoluble material was removed by filtration through diatomaceous earth and the filtrate was evaporated. The residue was purified by column chromatography using a Diaion HP20SS resin column, eluting with water and then with dilute aqueous hydrochloric acid (pH2). The fractions containing product were concentrated by evaporation and the resultant precipitate was collected by filtration and dried under vacuum over phosphorus pentoxide. There was thus obtained 2-amino-5-methoxy-4-(3-pyrrolidin-1-ylpropoxy)benzamide hydrochloride (1.44 g); NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 1.9 (br s, 2H), 2.05 (br s, 2H), 2.2 (br s, 2H), 3.05 (br s, 2H), 3.3 (t, 2H), 3.61 (br s, 2H), 3.8 (s, 3H), 4.11 (t, 2H), 7.05 (s, 1H), 7.53 (s, 1H).

After repetition of the previous reaction, a mixture of 2-amino-5-methoxy-4-(3-pyrrolidin-1-ylpropoxy)benzamide hydrochloride (5.92 g), Gold's reagent (3.5 g) and dioxane (50 ml) was heated to reflux for 5 hours. Acetic acid (0.7 ml) and sodium acetate (1.33 g) were added and the reaction mixture was heated to reflux for a further 5 hours. The mixture was allowed to cool to ambient temperature and evaporated. The residue was dissolved in water, adjusted to pH8 with 2N aqueous sodium hydroxide solution and purified on a Diaion HP20SS resin column eluting with methanol (gradient 0-50 %) in water. The fractions containing product were concentrated by evaporation and then freeze dried to give 6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)-3,4-dihydroquinazolin-4-one (4.55 g); NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 1.9 (m, 2H), 2.0-2.1 (m, 2H), 2.2-2.3 (m, 2H), 3.05 (m, 2H), 3.34 (t, 2H), 3.6-3.7 (br s, 2H), 3.94 (s, 3H), 4.27 (t, 2H), 7.31 (s, 1H), 7.55 (s, 1H), 9.02 (s, 1H).

A mixture of a portion (1.7 g) of the material so obtained, thionyl chloride (25 ml) and DMF (0.2 ml) was heated at reflux for 3 hours. Excess thionyl chloride was removed by evaporation and by azeotroping with toluene (x2). The residue was suspended in diethyl ether and washed with a 10% aqueous solution of sodium bicarbonate. The organic layer was dried over magnesium sulphate and evaporated to give 4-chloro-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (1.94 g); NMR Spectrum: ($CDCl_3$) 1.8 (br s, 4H), 2.17 (m, 2H), 2.6 (br s, 4H), 2.7 (t, 2H), 4.05 (s, 3H), 4.3 (t, 2H), 7.35 (s, 1H), 7.38 (s, 1H), 8.86 (s, 1H).

[2] The procedure of Example 3 was followed. The product gave the following characterising data: NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.35 (m, 2H), 3.5 (m, 2H), 3.7

(m, 4H), 3.8 (s, 3H), 3.85 (m, 4H), 4.0 (s, 3H), 4.35 (m, 2H), 7.05 (m, 1H), 7.2 (d, 1H), 7.4 (s, 1H), 7.6 (d, 1H), 8.2 (s, 1H), 8.85 (s, 1H); Mass Spectrum: $M+H^+$ 507 and 509.

The 4-chloro-7-[3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy]-6-methoxyquinazoline used as a starting material was prepared as follows :-

A mixture of 2-amino-4-benzyloxy-5-methoxybenzamide (J. Med. Chem., 1977, 20, 146-149; 10 g), (3-dimethylamino-2-azaprop-2-en-1-ylidene)dimethylammonium chloride (Gold's reagent, 7.4 g) and dioxane (100 ml) was stirred and heated to reflux for 24 hours. Sodium acetate (3.02 g) and acetic acid (1.65 ml) were added and the reaction mixture was heated for a further 3 hours. The mixture was evaporated and water was added to the residue. The resultant solid was collected by filtration, washed with water and dried. The material was recrystallised from acetic acid to give 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (8.7 g).

After repetition of the reaction so described, a mixture of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (35 g), thionyl chloride (440 ml) and DMF (1.75 ml) was heated to reflux for 4 hours. The thionyl chloride was evaporated under vacuum and the residue was azeotroped with toluene three times. The residue was dissolved in N-methylpyrrolidin-2-one (250 ml) to give a solution of 7-benzyloxy-4-chloro-6-methoxyquinazoline.

A mixture of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (20.3 g), thionyl chloride (440 ml) and DMF (1.75 ml) was heated to reflux for 4 hours. The thionyl chloride was evaporated under vacuum and the residue was azeotroped with toluene three times to give 7-benzyloxy-4-chloro-6-methoxyquinazoline.

A mixture of the 7-benzyloxy-4-chloro-6-methoxyquinazoline so obtained, potassium carbonate (50 g) and 4-chloro-2-fluorophenol (8.8 ml) and DMF (500 ml) was stirred and heated to 100°C for 5 hours. The mixture was allowed to cool to ambient temperature, poured into water (2 L) and stirred at ambient temperature for a few minutes. The resultant solid was isolated and washed with water. The solid was dissolved in methylene chloride and the solution was filtered and treated with decolourising charcoal. The resultant solution was filtered and evaporated to give a solid which was triturated under diethyl ether. There was thus obtained 7-benzyloxy-4-(4-chloro-2-fluorophenoxy)-6-methoxyquinazoline (23.2 g); NMR Spectrum: ($DMSOd_6$) 3.98 (s, 3H), 5.34 (s, 2H), 7.42 (m, 9H), 7.69 (m, 1H), 8.55 (s, 1H).

A mixture of the material so obtained and trifluoroacetic acid (15 ml) was heated to reflux for 3 hours. The reaction mixture was allowed to cool, toluene was added and the

mixture was evaporated. The residue was triturated under diethyl ether and then under acetone. The resultant precipitate was isolated and dried to give 4-(4-chloro-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline trifluoroacetate salt (21.8 g) which was used without further purification.

3-(1,1-Dioxotetrahydro-4H-1,4-thiazin-4-yl)propan-1-ol (4.2 g) and 1,1'-(azodicarbonyl)dipiperidine (11.7 g) were added in turn to a mixture of 4-(4-chloro-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline (5.0 g), tributylphosphine (11.1 ml) and methylene chloride (150 ml). The resultant mixture was stirred at ambient temperature overnight. The mixture was diluted with diethyl ether (300 ml) and the precipitate was removed by filtration. The filtrate was evaporated and the residue was purified by column chromatography on silica using a 19:1 mixture of methylene chloride and methanol as eluent. The material so obtained was triturated under ethyl acetate and dried to give 4-(4-chloro-2-fluorophenoxy)-7-[3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy]-6-methoxyquinazoline (5.4 g); NMR Spectrum: ($DMSOd_6$) 1.86 (m, 2H), 2.65 (t, 2H), 2.92 (m, 4H), 3.08 (m, 4H), 3.97 (s, 3H), 4.26 (t, 2H), 7.4 (m, 1H), 7.42 (s, 1H), 7.56 (m, 2H), 7.68 (m, 1H), 8.54 (s, 1H).

A mixture of a portion (3.5 g) of the material so obtained and a 2N aqueous hydrochloric acid solution (56 ml) was stirred and heated to 95°C for 2 hours. The reaction mixture was cooled to ambient temperature and treated with solid sodium bicarbonate to give a thick paste which was diluted with water and filtered. The solid was transferred to a flask and azeotroped with toluene twice to give a dry solid. The solid was purified by column chromatography on silica using a 19:1 mixture of methylene chloride and methanol as eluent. There was thus obtained 7-[3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy]-6-methoxy-3,4-dihydroquinazolin-4-one (2.26 g) as a white solid; Mass Spectrum: $M+H^+$ 368.

After repetition of the previous reaction, a mixture of 7-[3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy]-6-methoxy-3,4-dihydroquinazolin-4-one (4.2 g), thionyl chloride (45 ml) and DMF (0.1 ml) was heated to reflux for 2.5 hours. The residue was diluted with toluene and was evaporated under vacuum. The residue was taken up in water and basified to pH8 with a saturated aqueous sodium bicarbonate solution. The mixture was extracted with methylene chloride and the organic layer was washed in turn with water and brine. The organic solution was filtered through phase separating paper and evaporated to give an orange solid which was purified by column chromatography on silica using a 19:1 mixture of methylene chloride and methanol as eluent. The resultant solid was triturated

under diethyl ether and dried to give 4-chloro-7-[3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy]-6-methoxyquinazoline (2.27 g); Mass Spectrum: $M+H^+$ 386.

The 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propan-1-ol used as an intermediate was obtained as follows :-

A mixture of 3-aminopropan-1-ol (0.65 ml) and divinyl sulphone (1 g) was heated to 110°C for 45 minutes. The mixture was allowed to cool to ambient temperature and was purified by column chromatography on silica using a 19:1 mixture of methylene chloride and methanol as eluent. There was thus obtained 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propan-1-ol (0.8 g); NMR Spectrum: ($CDCl_3$) 1.7-1.8 (m, 2H), 2.73 (t, 2H), 3.06 (br s, 8H), 3.25 (s, 1H), 3.78 (t, 2H); Mass Spectrum: $M+H^+$ 194.

[3] The procedure of Example 3 was followed. The reaction product so obtained was mixed with methylene chloride (5 ml) and a saturated methanolic ammonia solution (0.5 ml) was added. The mixture was stirred at ambient temperature for 10 minutes. The mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography on silica using a 3:1 mixture of methylene chloride and a saturated methanolic ammonia solution as eluent. The material so obtained was dissolved in diethyl ether and a 2.9M solution of hydrogen chloride in diethyl ether (0.5 ml) was added. The mixture was evaporated and the residue was triturated under diethyl ether. The resultant solid was isolated, washed with diethyl ether and dried under vacuum. There was thus obtained the dihydrochloride salt of the required compound which gave the following characterising data: NMR Spectrum: ($DMSOd_6$) 1.4-1.5 (m, 2H), 1.7-1.8 (m, 3H), 2.0 (d, 2H), 2.75 (s, 3H), 2.95 (m, 2H), 3.4 (m, 2H), 3.8 (s, 3H), 3.95 (s, 3H), 4.2 (m, 2H), 6.92 (m, 1H), 7.12 (d, 1H), 7.22 (s, 1H), 7.5 (d, 1H), 7.85 (s, 1H), 8.32 (s, 1H), 9.6 (m, 1H); Mass Spectrum: $M+H^+$ 457 and 459.

[4] 7-[2-(N-tert-Butoxycarbonylpiperidin-4-yl)ethoxy]-4-chloro-6-methoxyquinazoline was used as the appropriate 4-chloroquinazoline and the procedure of Example 2 was followed. The product was obtained as the monohydrochloride salt and gave the following characterising data: NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 1.88 (br s, 3H), 2.0 (d, 2H), 2.95 (m, 2H), 3.32 (d, 2H), 3.83 (s, 3H), 4.02 (s, 3H), 4.3 (m, 2H), 7.02 (m, 1H), 7.20 (d, 1H), 7.38 (s, 1H), 7.72 (d, 1H), 8.16 (s, 1H), 8.85 (s, 1H); Mass Spectrum: $M-H^-$ 485 and 487.

The 7-[2-(N-tert-butoxycarbonylpiperidin-4-yl)ethoxy]-4-chloro-6-methoxyquinazoline used as a starting material was obtained as follows :-

A mixture of 7-hydroxy-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (2 g), N-tert-butoxycarbonyl-4-[2-(4-toluenesulphonyloxy)ethyl]piperidine (2.84 g), potassium carbonate (1.8 g) and DMF (20 ml) was stirred and heated to 95°C for 2.5 hours. The resultant mixture was cooled to ambient temperature and poured onto a mixture of ice and water. The mixture was extracted with methylene chloride. The organic layer was washed with brine, dried over magnesium sulphate and evaporated. There was thus obtained 7-[2-(N-tert-butoxycarbonylpiperidin-4-yl)ethoxy]-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (2 g); NMR Spectrum: ($DMSOd_6$) 1.0-1.15 (m, 2H), 1.15 (s, 9H), 1.4 (s, 9H), 1.6-1.8 (m, 3H), 2.6-2.8 (m, 2H), 3.92 (s, 3H), 3.9-4.0 (m, 2H), 4.2 (m, 2H), 5.92 (s, 2H), 7.2 (s, 1H), 7.5 (s, 1H), 8.3 (s, 1H).

Using an analogous procedure to that described in the fourth paragraph of the portion of Example 2 that is concerned with the preparation of starting materials, 7-[2-(N-tert-butoxycarbonylpiperidin-4-yl)ethoxy]-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (2 g) was treated with a saturated methanolic ammonia solution to give 7-[2-(N-tert-butoxycarbonylpiperidin-4-yl)ethoxy]-6-methoxy-3,4-dihydroquinazolin-4-one (1.3 g); NMR Spectrum: ($DMSOd_6$) 1.0-1.15 (m, 2H), 1.4 (s, 9H), 1.6-1.8 (m, 3H), 2.6-2.8 (m, 2H), 3.3-3.5 (m, 2H), 3.9 (s, 3H), 3.9-4.0 (m, 2H), 4.18 (m, 2H), 7.15 (s, 1H), 7.45 (s, 1H), 8.0 (s, 1H); Mass Spectrum: $M+H^+$ 404.

Using an analogous procedure to that described in the fifth paragraph of the portion of Example 2 that is concerned with the preparation of starting materials, 7-[2-(N-tert-butoxycarbonylpiperidin-4-yl)ethoxy]-6-methoxy-3,4-dihydroquinazolin-4-one (0.2 g) was reacted with carbon tetrachloride and triphenylphosphine to give 7-[2-(N-tert-butoxycarbonylpiperidin-4-yl)ethoxy]-4-chloro-6-methoxyquinazoline (0.03 g); NMR Spectrum: ($DMSOd_6$) 1.0-1.2 (m, 2H), 1.4 (s, 9H), 1.6-1.8 (m, 5H), 2.6-2.8 (m, 2H), 3.92 (d, 2H), 4.0 (s, 3H), 4.3 (m, 2H), 7.4 (s, 1H), 7.5 (s, 1H), 8.9 (s, 1H).

The N-tert-butoxycarbonyl-4-[2-(4-toluenesulphonyloxy)ethyl]piperidine used as a starting material was prepared by the reaction of 4-toluenesulphonyl chloride with N-tert-butoxycarbonyl-4-(2-hydroxyethyl)piperidine (International Patent Application WO 00/47212, in example 126 thereof) using an analogous procedure to that described in the third paragraph of the portion of Example 1 that is concerned with the preparation of starting materials.

[5] 7-(N-tert-Butoxycarbonylpiperidin-4-ylmethoxy)-4-chloro-6-methoxyquinazoline was used as the appropriate 4-chloroquinazoline and the procedure of Example 2 was followed.

The product was obtained as the monohydrochloride salt and gave the following characterising data: NMR Spectrum: ($DMSOd_6$) 1.5-1.7 (m, 2H), 1.95-2.05 (m, 2H), 2.15-2.25 (m, 1H), 2.9-3.05 (m, 2H), 3.3-3.4 (m, 2H), 3.8 (s, 3H), 4.05 (s, 3H), 4.12 (d, 2H), 7.03 (m, 1H), 7.18 (d, 1H), 7.45 (s, 1H), 7.72 (d, 1H), 8.28 (s, 1H), 8.7 (br s, 1H), 8.8 (s, 1H), 9.05 (br s, 1H); Mass Spectrum: $M+H^+$ 473 and 475.

[6] The procedure of Example 3 was followed. The product gave the following characterising data: Mass Spectrum: $M+H^+$ 559 and 561.

The 7-(2-acetoxy-3-piperidinopropoxy)-4-chloro-6-methoxyquinazoline used as a starting material was prepared as follows :-

A mixture of 7-hydroxy-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (40 g), 2,3-epoxypropyl bromide (16.8 ml), potassium carbonate (36 g) and DMF (400 ml) was stirred and heated to 70°C for 1.5 hours. The mixture was poured into an ice-water mixture (1.5 L) and the resultant precipitate was isolated, washed in turn with water and diethyl ether and dried under vacuum over phosphorus pentoxide. There was thus obtained 7-(2,3-epoxypropoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (46.7 g).

A mixture of a portion (8 g) of the material so obtained, piperidine (2.4 ml) and chloroform (120 ml) was heated to reflux for 16 hours. The mixture was evaporated and the residue was purified by column chromatography on silica using a 19:1 mixture of methylene chloride and methanol as eluent. There was thus obtained 7-(2-hydroxy-3-piperidinopropoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one as a solid (9.2 g); NMR Spectrum: ($DMSOd_6$) 1.1 (s, 9H), 1.5 (m, 6H), 2.4 (m, 6H), 3.9 (s, 3H), 4.05 (m, 2H), 4.15 (m, 1H), 4.9 (br s, 1H), 5.9 (s, 2H), 7.2 (s, 1H), 7.5 (s, 1H), 8.35 (s, 1H).

A mixture of the material so obtained and a saturated methanolic ammonia solution (240 ml) was stirred at ambient temperature for 48 hours. The mixture was evaporated and the resultant solid was washed with a 19:1 mixture of diethyl ether and methylene chloride. There was thus obtained 7-(2-hydroxy-3-piperidinopropoxy)-6-methoxy-3,4-dihydroquinazolin-4-one (6.2 g); NMR Spectrum: ($DMSOd_6$ & CF_3CO_2D) 1.4 (m, 1H), 1.7 (m, 2H), 1.8 (m, 3H), 3.0 (m, 2H), 3.35 (m, 2H), 3.5 (m, 2H), 3.9 (s, 3H), 4.15 (d, 2H), 4.4 (m, 1H), 7.3 (s, 1H), 7.55 (s, 1H), 8.75 (s, 1H).

A mixture of a portion (5.6 g) of the material so obtained and acetic anhydride (8.25 ml) was stirred at ambient temperature for 1.3 hours. Water (3 ml) was added and the resultant mixture was cooled in an ice-bath and basified to pH9.5 by the addition of a 2N aqueous sodium hydroxide solution. The mixture was extracted with methylene chloride and

the organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated. There was thus obtained 7-(2-acetoxy-3-piperidinopropoxy)-6-methoxy-3,4-dihydroquinazolin-4-one as a solid (4.8 g) which was used without further purification.

A mixture of the material so obtained, thionyl chloride (62 ml) and DMF (0.7 ml) was heated to reflux for 1.5 hours. The mixture was evaporated, toluene was added and the mixture was evaporated. Methylene chloride followed by a mixture of ice and water were added to the residue and the mixture was basified to pH7.5 by the addition of a saturated aqueous sodium bicarbonate solution and to pH9 by the addition of a 2N aqueous sodium hydroxide solution. The organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated. The residue was triturated under diethyl ether. There was thus obtained 7-(2-acetoxy-3-piperidinopropoxy)-4-chloro-6-methoxyquinazoline; NMR Spectrum: ($CDCl_3$ and CD_3CO_2D) 1.6 (m, 2H), 1.9 (m, 4H), 2.1 (s, 3H), 3.2 (br s, 4H), 3.5 (m, 2H), 4.05 (s, 3H), 4.35 (m, 2H), 5.7 (m, 1H), 7.4 (s, 1H), 7.5 (s, 1H), 8.9 (s, 1H).

[7] The procedure of Example 3 was followed. The product gave the following characterising data: Mass Spectrum: $M+H^+$ 599 and 601.

The 7-[2-acetoxy-3-(4-cyanomethylpiperazin-1-yl)propoxy]-4-chloro-6-methoxyquinazoline used as a starting material was prepared as follows :-

7-(2,3-Epoxypropoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one was reacted with 1-cyanomethylpiperazine using an analogous procedure to that described in the second paragraph of the portion of Note [6] immediately above that is concerned with the preparation of starting materials. There was thus obtained 7-[3-(4-cyanomethylpiperazin-1-yl)-2-hydroxypropoxy]-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one.

The material so obtained was taken through an analogous sequence of reactions to those described in the third to fifth paragraphs of the portion of Note [6] immediately above that is concerned with the preparation of starting materials. There was thus obtained 7-[2-acetoxy-3-(4-cyanomethylpiperazin-1-yl)propoxy]-4-chloro-6-methoxyquinazoline; NMR Spectrum: ($CDCl_3$) 2.1 (s, 3H), 2.65 (br s, 10H), 3.5 (s, 2H), 4.05 (s, 3H), 4.4 (m, 2H), 5.45 (m, 1H), 7.25 (s, 1H), 7.4 (s, 1H), 8.85 (s, 1H); Mass Spectrum: $M+H^+$ 434 and 436.

The 1-cyanomethylpiperazine used as a starting material was prepared as follows :-

A mixture of 1-(tert-butoxycarbonyl)piperazine (5 g), 2-chloroacetonitrile (1.9 ml), potassium carbonate (4 g) and DMF (20 ml) was stirred at ambient temperature for 16 hours. A saturated aqueous ammonium chloride solution was added and the mixture was extracted with ethyl acetate. The organic phase was dried over magnesium sulphate and evaporated.

The residue was purified by column chromatography on silica using diethyl ether as eluent. There was thus obtained 1-(tert-butoxycarbonyl)-4-cyanomethylpiperazine as a solid (5.7 g); NMR Spectrum: ($CDCl_3$) 1.45 (s, 9H), 2.5 (m, 4H), 3.45 (m, 4H), 3.55 (s, 2H).

A mixture of the material so obtained, trifluoroacetic acid (20 ml) and methylene chloride (25 ml) was stirred at ambient temperature for 4 hours. The mixture was evaporated, toluene was added and the mixture was evaporated again. The residue was purified by column chromatography on silica using a 9:1 mixture of methylene chloride and methanol as eluent. There was thus obtained 1-cyanomethylpiperazine trifluoroacetate salt which was treated with solid sodium bicarbonate in a mixture of methylene chloride, ethyl acetate and methanol to give the free base form (2.9 g); NMR Spectrum: ($CDCl_3$ and $DMSOd_6$) 2.7 (m, 4H), 3.2 (m, 4H), 3.6 (s, 2H), 6.2 (br s, 1H).

Example 5 **4-(2-chloro-5-methoxyanilino)-6-methoxy-7-[2-(4-pyridyloxy)ethoxy]quinazoline**

Diethyl azodicarboxylate (0.142 ml) was added dropwise to a stirred mixture of 4-(2-chloro-5-methoxyanilino)-7-hydroxy-6-methoxyquinazoline (0.2 g), 2-(4-pyridyloxy)ethanol (0.08 g), triphenylphosphine (0.19 g) and methylene chloride (8 ml) and the reaction mixture was stirred at ambient temperature for 1 hour. The mixture was evaporated and the residue was purified by column chromatography on silica using a 19:1 mixture of methylene chloride and methanol as eluent. There was thus obtained the title compound (0.158 g); NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 3.8 (s, 3H), 4.0 (s, 3H), 4.7 (m, 2H), 4.9 (m, 2H), 7.1 (m, 1H), 7.2 (d, 1H), 7.45 (s, 1H), 7.6 (d, 1H), 7.7 (d, 2H), 8.15 (s, 1H), 8.85 (m, 3H); Mass Spectrum: $M+H^+$ 453 and 455.

The 4-(2-chloro-5-methoxyanilino)-7-hydroxy-6-methoxyquinazoline used as a starting material was obtained as follows :-

A mixture of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (35 g), thionyl chloride (440 ml) and DMF (1.75 ml) was heated to reflux for 4 hours. The thionyl chloride was evaporated under vacuum and the residue was azeotroped with toluene three times. The residue was dissolved in N-methylpyrrolidin-2-one (250 ml) to give a solution of 7-benzyloxy-4-chloro-6-methoxyquinazoline.

A mixture of 7-benzyloxy-4-chloro-6-methoxyquinazoline (4.3 g), 2-chloro-5-methoxyaniline (2.7 g), a 6.2M solution of hydrogen chloride in isopropanol (0.225 ml) and isopropanol (200 ml) was stirred and heated to 80°C for 2.5 hours. The mixture was cooled to

0°C and the precipitate was isolated, washed with in turn with isopropanol and diethyl ether and dried under vacuum. There was thus obtained 7-benzyloxy-4-(2-chloro-5-methoxyanilino)-6-methoxyquinazoline (4.73 g); NMR Spectrum: ($DMSOd_6$) 3.8 (s, 3H), 4.03 (s, 3H), 5.36 (s, 2H), 7.06 (m, 1H), 7.18 (d, 1H), 7.4-7.6 (m, 7H), 8.2 (s, 1H), 8.77 (s, 1H), 11.5 (br s, 1H); Mass Spectrum: $M+H^+$ 422 and 424.

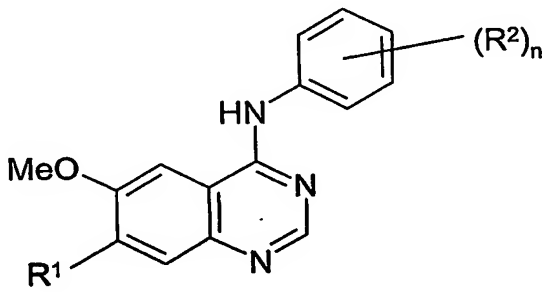
A mixture of the material so obtained and trifluoroacetic acid (40 ml) was stirred and heated to 80°C for 4 hours. The mixture was poured into water and solid sodium bicarbonate was added to basify the mixture to pH8. The resultant precipitate was isolated, washed with water and dried under vacuum at 50°C for 48 hours. The material so obtained was purified by column chromatography on silica using a 1:1 mixture of methylene chloride and ethyl acetate as eluent. There was thus obtained 4-(2-chloro-5-methoxyanilino)-7-hydroxy-6-methoxyquinazoline (2.9 g); NMR Spectrum: ($DMSOd_6$) 3.8 (s, 3H), 4.0 (s, 3H), 6.95 (m, 1H), 7.1 (s, 1H), 7.15 (s, 1H), 7.5 (d, 1H), 7.8 (s, 1H), 8.3 (s, 1H), 9.5 (br s, 1H), 10.4 (br s, 1H).

The 2-(4-pyridyloxy)ethanol used as a starting material was prepared using an analogous procedure to that described in J. Chem. Soc. Perkin II, 1987, 1867.

Example 6

Using an analogous procedure to that described in Example 5, the appropriate 7-hydroxyquinazoline was reacted with the appropriate alcohol to give the compounds described in Table II. Unless otherwise stated, each compound described in Table II was obtained as a free base.

Table II



Compound No. & Note	R^1	$(R^2)_n$
[1]	3-(4-pyridyloxy)propoxy	2-chloro-5-methoxy
[2]	2-(4-pyridyloxy)ethoxy	2-bromo-5-methoxy
[3]	3-(4-pyridyloxy)propoxy	2-bromo-5-methoxy
[4]	3-(2-pyridyloxy)propoxy	2-chloro-5-methoxy
[5]	2-cyanopyrid-4-ylmethoxy	2-chloro-5-methoxy
[6]	2-cyanopyrid-4-ylmethoxy	2-bromo-5-methoxy
[7]	2-(5-methyl-2-morpholinomethylimidazol-1-yl)ethoxy	2-chloro-5-methoxy

Notes

[1] The product gave the following characterising data: NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.4 (m, 2H), 3.8 (s, 3H), 4.0 (s, 3H), 4.4 (m, 2H), 4.6 (m, 2H), 7.1 (m, 1H), 7.2 (d, 1H), 7.4 (s, 1H), 7.6 (m, 3H), 8.1 (s, 1H), 8.8 (d, 2H), 8.85 (s, 1H); Mass Spectrum: $M\text{-}H^-$ 465 and 467.

The 3-(4-pyridyloxy)propanol used as a starting material was prepared as follows :-

Sodium hydroxide (6.66 g) was added to a stirred mixture of 4-chloropyridine hydrochloride (10 g), 1,3-propanediol (24 ml) and DMSO (100 ml) and the resultant mixture was heated to 100°C for 20 hours. The mixture was evaporated and the residue was poured into an ice-water mixture and extracted with ethyl acetate The organic solution was dried over magnesium sulphate and evaporated. The material so obtained was purified by column chromatography on silica using increasingly polar solvent mixtures of methylene chloride, ethyl acetate and methanol as eluent. There was thus obtained 3-(4-pyridyloxy)propanol (3.13 g); NMR Spectrum: ($CDCl_3$) 2.05 (m, 2H), 2.95 (br s, 1H), 3.85 (m, 2H), 4.15 (t, 2H), 6.8 (d, 2H), 8.35 (d, 2H).

[2] The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 3.8 (s, 3H), 4.0 (s, 3H), 4.7 (m, 2H), 4.9 (m, 2H), 7.1 (m, 1H), 7.2 (d, 1H), 7.45 (s, 1H), 7.7 (m, 3H), 8.15 (s, 1H), 8.85 (m, 3H); Mass Spectrum: $M+H^+$ 497 and 499.

[3] The product gave the following characterising data: NMR Spectrum: ($DMSOd_6$) 2.3 (m, 2H), 3.8 (s, 3H), 4.0 (s, 3H), 4.3 (m, 4H), 6.9 (m, 1H), 7.05 (d, 2H), 7.15 (s, 1H), 7.25 (s, 1H), 7.65 (d, 1H), 7.85 (s, 1H), 8.35 (s, 1H), 8.4 (d, 2H), 9.5 (s, 1H); Mass Spectrum: $M\text{-}H^-$ 509 and 511.

[4] The product gave the following characterising data: NMR Spectrum: ($DMSOd_6$) 2.2 (m, 2H), 3.8 (s, 3H), 3.95 (s, 3H), 4.05 (t, 2H), 4.15 (t, 2H), 6.2 (t, 1H), 6.4 (d, 1H), 6.9 (m, 1H), 7.15 (d, 1H), 7.17 (s, 1H), 7.4 (m, 1H), 7.5 (d, 1H), 7.65 (m, 1H), 7.85 (s, 1H), 8.3 (s, 1H), 9.5 (s, 1H); Mass Spectrum: $M+H^+$ 467 and 469.

The 3-(2-pyridyloxy)propanol used as a starting material is described in Bull. Soc. Chim. Fr., 1970, 637.

[5] The product gave the following characterising data: NMR Spectrum: ($DMSOd_6$) 3.8 (s, 3H), 4.05 (s, 3H), 5.5 (s, 2H), 6.95 (m, 1H), 7.15 (d, 1H), 7.3 (s, 1H), 7.5 (d, 1H), 7.85 (m, 1H), 7.95 (s, 1H), 8.15 (s, 1H), 8.35 (s, 1H), 8.85 (d, 1H), 9.6 (br s, 1H); Mass Spectrum: $M+H^+$ 448 and 450.

The 2-cyano-4-hydroxymethylpyridine used as a starting material was prepared as follows :-

Using an analogous procedure to that disclosed in J. Het. Chem., 1993, 30, 631, 4-hydroxymethylpyridine was converted into 4-(tert-butyldimethylsilyloxymethyl)pyridine-2-carbonitrile.

A mixture of the material so obtained (3.37 g) tert-butylammonium fluoride (1M solution in THF; 24 ml) and THF (20 ml) was stirred at ambient temperature for 1 hour. The mixture was evaporated and the residue was partitioned between ethyl acetate and a saturated aqueous ammonium chloride solution. The organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of petroleum ether (b.p. 40-60°C) and ethyl acetate as eluent. There was thus obtained 2-cyano-4-hydroxymethylpyridine as a solid (1.37 g); NMR Spectrum: ($CDCl_3$) 2.25 (br s, 1H), 4.85 (s, 2H), 7.55 (d, 1H), 7.75 (s, 1H), 8.7 (d, 1H).

[6] The product gave the following characterising data: NMR Spectrum: ($DMSOd_6$) 3.8 (s, 3H), 4.05 (s, 3H), 5.5 (s, 2H), 6.9 (m, 1H), 7.15 (d, 1H), 7.3 (s, 1H), 7.65 (d, 1H), 7.85 (m, 1H), 7.95 (s, 1H); 8.15 (s, 1H), 8.35 (s, 1H), 8.85 (d, 1H), 9.6 (br s, 1H); Mass Spectrum: $M+H^+$ 492 and 494.

[7] The product gave the following characterising data: NMR Spectrum: ($DMSOd_6$) 2.3 (s, 3H), 2.35 (br s, 4H), 3.55 (br s, 4H), 3.65 (s, 2H), 3.8 (s, 3H), 3.95 (s, 3H), 4.5 (br s, 4H), 6.5 (s, 1H), 6.9 (m, 1H), 7.15 (d, 1H), 7.2 (s, 1H), 7.5 (d, 1H), 7.8 (s, 1H), 8.3 (s, 1H), 9.5 (s, 1H); Mass Spectrum: $M+H^+$ 539 and 541.

The 1-(2-hydroxyethyl)-5-methyl-2-morpholinomethylimidazole used as a starting material was prepared as follows :-

A mixture of 4-methyl-1-tritylimidazole (J. Heterocyclic Chem., 1982, 19, 253; 32.5 g), methyl bromoacetate (11.4 ml) and acetone (500 ml) was heated to reflux for 2 hours. The solvent was removed by evaporation and the residue was dissolved in methanol (100 ml) and heated to reflux for 45 minutes. The mixture was evaporated and the residue was triturated under diethyl ether. The resultant precipitate was isolated and stirred at ambient temperature for 1 hour in a mixture of diethyl ether (200 ml) and a saturated methanolic ammonia solution (20 ml). The mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography on silica using a 49:1 mixture of methylene chloride and methanol as eluent. There was thus obtained methyl 2-(5-methylimidazol-1-yl)acetate (6 g); NMR Spectrum: ($CDCl_3$) 2.16 (s, 3H), 3.78 (s, 3H), 4.61 (s, 3H), 6.8 (s, 1H), 7.42 (s, 1H).

A solution of a portion (1.7 g) of the material so obtained in diethyl ether (20 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (0.76 g) in diethyl ether (70 ml) which was cooled to 0°C. The resultant mixture was stirred at ambient temperature for 1 hour. The mixture was cooled to 0°C and a 6N aqueous sodium hydroxide solution (0.8 ml) and water (2.4 ml) were added dropwise in turn. The mixture was stirred at ambient temperature for 30 minutes and then evaporated. The residue was dissolved in methylene chloride, dried over magnesium sulphate and evaporated to give 1-(2-hydroxyethyl)-5-methylimidazole (1.1 g); NMR Spectrum: ($CDCl_3$) 2.17 (s, 3H), 3.81 (t, 2H), 3.92 (t, 2H), 6.6 (s, 1H), 7.24 (s, 1H).

Tert-butyldimethylsilyl chloride (9.05 g) was added to a stirred mixture of 1-(2-hydroxyethyl)-5-methylimidazole (6.4 g), imidazole (7.5 g) and methylene chloride (30 ml) which was cooled to 0°C. The reaction mixture was stirred at ambient temperature for 4 hours. The mixture was poured into water. The organic layer was washed with brine, dried over magnesium sulphate and evaporated to give 1-(2-tert-butyldimethylsilyloxyethyl)-5-methylimidazole (11.7 g); NMR Spectrum: ($CDCl_3$) -0.04 (s, 6H), 0.85 (s, 6H), 2.2 (s, 3H), 3.8 (m, 2H), 3.94 (m, 2H), 6.75 (s, 1H), 7.43 (s, 1H).

The material so obtained was dissolved in THF (400 ml) and the solution was cooled at -60°C. n-Butyllithium (2.5M in hexane, 40 ml) was added dropwise and the mixture was stirred at -50°C for 1 hour. The mixture was cooled to -60°C and DMF (12.5 ml) was added dropwise. The resultant mixture was allowed to warm to ambient temperature and was stirred

for 2 hours. Diethyl ether (500 ml) was added and the reaction mixture was poured into a saturated aqueous ammonium chloride solution. The organic layer was separated, washed with brine, dried over magnesium sulphate and evaporated. The material so obtained was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and a saturated methanolic ammonia solution as eluent. There was thus obtained 1-(2-tert-butyldimethylsilyloxyethyl)-2-formyl-5-methylimidazole (11 g); NMR Spectrum: ($CDCl_3$) -0.1 (s, 6H), 0.79 (s, 9H), 2.32 (s, 3H), 3.91 (t, 2H), 4.4 (t, 2H), 7.07 (s, 1H), 9.71 (s, 1H).

A portion (0.79 g) of the material so obtained was dissolved in methylene chloride (24 ml) and morpholine (0.263 ml) and acetic acid (0.175 ml) were added. Sodium borohydride triacetate (0.8 g) was added portionwise and the mixture was stirred at ambient temperature for 16 hours. The mixture was evaporated and the residue was purified by column chromatography on silica using a 49:1 mixture of methylene chloride and a saturated methanolic ammonia solution as eluent. There was thus obtained 1-(2-tert-butyldimethylsilyloxyethyl)-5-methyl-2-morpholinomethylimidazole (0.5 g); NMR Spectrum: ($CDCl_3$) 0 (s, 6H), 0.82 (s, 9H), 2.25 (s, 3H), 2.45 (m, 4H), 3.6 (s, 2H), 3.68 (m, 4H), 3.85 (t, 2H), 4.1 (t, 2H), 6.7 (s, 1H).

A mixture of the material so obtained, 12N aqueous hydrochloric acid (0.26 ml) and methanol (10 ml) was stirred at ambient temperature for 5 hours. The mixture was evaporated and the residue was triturated under pentane. The resultant solid was isolated and dried under vacuum. The solid was stirred at ambient temperature for 1 hour in a mixture of methylene chloride and a saturated methanolic ammonia solution. The mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography on silica using a 19:1 mixture of methylene chloride and a saturated methanolic ammonia solution as eluent. There was thus obtained 1-(2-hydroxyethyl)-5-methyl-2-morpholinomethylimidazole (0.25 g); NMR Spectrum: ($CDCl_3$) 2.2 (s, 3H), 2.6 (br s, 4H), 3.58 (s, 2H), 3.7 (m, 4H), 3.85 (t, 2H), 4.1 (t, 2H), 6.5-6.9 (br s, 1H), 6.65 (s, 1H).

Example 7 4-(2-chloro-5-methoxyanilino)-7-(2-hydroxy-3-pyrrolidin-1-ylpropoxy)-6-methoxyquinazoline

A mixture of 4-(2-chloro-5-methoxyanilino)-7-(2,3-epoxypropoxy)-6-methoxyquinazoline (0.1 g), pyrrolidine (0.02 g) and chloroform (3 ml) was stirred and heated to reflux for 5 hours. The mixture was evaporated and the residue was purified by

column chromatography on silica using a 4:5:1 mixture of methylene chloride, ethyl acetate and a saturated methanolic ammonia solution as eluent. There was thus obtained the title compound (0.008 g); NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 1.9-2.0 (m, 2H), 2.1-2.2 (m, 2H), 3.1-3.2 (m, 2H), 3.4 (m, 2H), 3.6-3.7 (m, 2H), 3.85 (s, 3H), 4.05 (s, 3H), 4.25 (d, 2H), 4.4 (m, 1H), 7.1 (d, 1H), 7.21 (d, 1H), 7.4 (s, 1H), 7.6 (d, 1H), 8.18 (s, 1H), 8.88 (s, 1H); Mass Spectrum: $M+H^+$ 459 and 461.

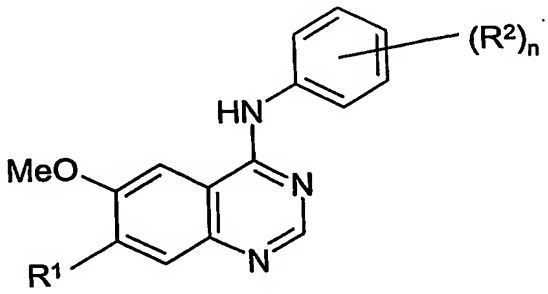
The 4-(2-chloro-5-methoxyanilino)-7-(2,3-epoxypropoxy)-6-methoxyquinazoline used as a starting material was prepared as follows :-

A mixture of 4-(2-chloro-5-methoxyanilino)-7-hydroxy-6-methoxyquinazoline (0.386 g), 2,3-epoxypropyl bromide (0.12 ml), potassium carbonate (0.321 g) and DMF (3 ml) was stirred and heated to 60°C for 2 hours. The mixture was cooled to ambient temperature and water (50 ml) was added. The resultant precipitate was isolated, washed with water and dried under vacuum at 55°C. The material so obtained was purified by column chromatography on silica using a 19:1 mixture of methylene chloride and methanol as eluent. There was thus obtained the required starting material (0.315 g); NMR Spectrum: ($DMSOd_6$) 2.78 (m, 1H), 2.9 (m, 1H), 3.45 (m, 1H), 3.8 (s, 3H), 3.95 (s, 3H), 4.0 (m, 1H), 4.53 (m, 1H), 6.92 (m, 1H), 7.15 (d, 1H), 7.2 (s, 1H), 7.5 (d, 1H), 7.85 (s, 1H), 8.32 (s, 1H), 9.52 (s, 1H); Mass Spectrum: $M+H^+$ 388 and 390.

Example 8

Using an analogous procedure to that described in Example 7, the appropriate 7-(2,3-epoxypropoxy)quinazoline was reacted with the appropriate heterocyclic compound or amine to give the compounds described in Table III. Unless otherwise stated, each compound described in Table III was obtained as a free base and as a racemate.

Table III



Compound No. & Note	R^1	$(R^2)_n$
[1]	2-hydroxy-3-(4-methylpiperazin-1-yl)propoxy	2-chloro-5-methoxy
[2]	2-hydroxy-3-morpholinopropoxy	2-chloro-5-methoxy
[3]	3-homopiperidin-1-yl-2-hydroxypropoxy	2-chloro-5-methoxy
[4]	3-[N-(2-cyanoethyl)-N-methylamino]-2-hydroxypropoxy	2-chloro-5-methoxy
[5]	3-(4-acetylpiperazin-1-yl)-2-hydroxypropoxy	2-chloro-5-methoxy
[6]	3-(N-allyl-N-methylamino)-2-hydroxypropoxy	2-chloro-5-methoxy
[7]	2-hydroxy-3-(N-isopropyl-N-methylamino)propoxy	2-chloro-5-methoxy
[8]	3-azetidin-1-yl-2-hydroxypropoxy	2-chloro-5-methoxy
[9]	3-(N-ethyl-N-isopropylamino)-2-hydroxypropoxy	2-chloro-5-methoxy
[10]	2-hydroxy-3-(2-methylpyrrolidin-1-yl)propoxy	2-chloro-5-methoxy
[11]	2-hydroxy-3-(1,2,5,6-tetrahydropyridin-1-yl)propoxy	2-chloro-5-methoxy
[12]	3-(4-cyclopropylpiperazin-1-yl)-2-hydroxypropoxy	2-chloro-5-methoxy
[13]	3-(4-allylpiperazin-1-yl)-2-hydroxypropoxy	2-chloro-5-methoxy

Notes

[1] The product gave the following characterising data: NMR Spectrum: ($DMSOd_6$) 2.18 (s, 3H), 2.2-2.5 (m, 10H), 3.8 (s, 3H), 3.95 (s, 3H), 4.05 (d, 1H), 4.2 (d, 1H), 4.95 (br s, 1H), 6.92 (d, 1H), 7.15 (s, 1H), 7.2 (s, 1H), 7.5 (d, 1H), 7.82 (s, 1H), 8.35 (s, 1H), 9.5 (s, 1H); Mass Spectrum: $M+H^+$ 488 and 490.

[2] The product gave the following characterising data: NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 3.15-3.48 (m, 4H), 3.55 (t, 2H), 3.7-3.9 (m, 2H), 3.82 (s, 3H), 4.0 (d, 2H), 4.05 (s, 3H), 4.28 (d, 2H), 4.5 (m, 1H), 7.1 (m, 1H), 7.22 (d, 1H), 7.42 (s, 1H), 7.6 (d, 1H), 8.18 (s, 1H), 8.88 (s, 1H); Mass Spectrum: $M+H^+$ 475 and 477.

[3] The reaction mixture was heated to 40°C for 3 hours rather than to reflux. The product gave the following characterising data: NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 1.5-1.75 (m, 4H), 1.8-2.0 (m, 4H), 3.3-3.4 (m, 3H), 3.4-3.55 (m, 3H), 3.81 (s, 3H), 4.01 (s, 3H), 4.23

(d, 2H), 4.45 (m, 1H), 7.1 (m, 1H), 7.2 (d, 1H), 7.45 (s, 1H), 7.6 (d, 1H), 8.14 (s, 1H), 8.86 (s, 1H); Mass Spectrum: $M+H^+$ 487 and 489.

[4] The reaction mixture was heated to 40°C for 3 hours rather than to reflux. The product gave the following characterising data: NMR Spectrum: ($DMSOd_6$) 2.3 (s, 3H), 2.45-2.75 (m, 6H), 3.8 (s, 3H), 3.98 (s, 3H), 4.0-4.1 (m, 2H), 4.2 (d, 1H), 5.0 (d, 1H), 6.92 (m, 1H), 7.15 (d, 1H), 7.2 (s, 1H), 7.5 (d, 1H), 7.82 (s, 1H), 8.32 (s, 1H), 9.5 (s, 1H); Mass Spectrum: $M+H^+$ 472 and 474.

[5] The reaction mixture was heated to 40°C for 3 hours rather than to reflux. The reaction product was triturated under diethyl ether to which was added two equivalents of a 2M solution of hydrogen chloride in isopropanol. There was thus obtained the dihydrochloride salt of the required product which gave the following characterising data: Mass Spectrum: $M+H^+$ 516 and 518.

[6] The reaction mixture was heated to 40°C for 3 hours rather than to reflux. The product gave the following characterising data: NMR Spectrum: ($DMSOd_6$) 2.25 (s, 3H), 2.3-2.5 (m, 2H), 3.0-3.15 (m, 2H), 3.8 (s, 3H), 3.98 (s, 3H), 4.0-4.1 (m, 2H), 4.2 (m, 1H), 4.92 (d, 1H), 5.1-5.25 (m, 2H), 5.8-5.9 (m, 1H), 6.93 (m, 1H), 7.18 (d, 1H), 7.2 (s, 1H), 7.5 (d, 1H), 7.85 (s, 1H), 8.35 (s, 1H), 9.5 (s, 1H); Mass Spectrum: $M+H^+$ 459 and 461.

[7] The reaction mixture was heated to 40°C for 3 hours rather than to reflux. The product gave the following characterising data: NMR Spectrum: ($DMSOd_6$) 0.95 (m, 6H), 2.25 (s, 3H), 2.4 (m, 2H), 2.8 (m, 1H), 3.8 (s, 3H), 3.9 (s, 3H), 3.9 (br s, 1H), 4.05 (m, 1H), 4.2 (m, 1H), 4.82 (br s, 1H), 6.95 (m, 1H), 7.15 (d, 1H), 7.2 (s, 1H), 7.5 (d, 1H), 7.82 (s, 1H), 8.32 (s, 1H), 9.5 (s, 1H); Mass Spectrum: $M+H^+$ 461 and 463.

[8] The reaction mixture was heated to 40°C for 3 hours rather than to reflux. The product gave the following characterising data: NMR Spectrum: ($DMSOd_6$) 2.0 (m, 2H), 2.45-2.55 (m, 2H), 3.2 (m, 4H), 3.8 (s, 3H), 3.8-3.9 (m, 1H), 3.98 (s, 3H), 4.03 (m, 1H), 4.12 (m, 1H), 4.92 (d, 1H), 6.95 (m, 1H), 7.18 (d, 1H), 7.2 (s, 1H), 7.5 (d, 1H), 7.82 (s, 1H), 8.35 (s, 1H), 9.5 (s, 1H); Mass Spectrum: $M+H^+$ 445 and 447.

[9] The reaction mixture was heated to 40°C for 3 hours rather than to reflux. The product gave the following characterising data: NMR Spectrum: ($DMSOd_6$) 0.9-1.05 (m, 9H), 2.35-2.5 (m, 2H), 2.55-2.65 (m, 2H), 2.95 (m, 1H), 3.8 (s, 3H), 3.9 (m, 1H), 3.98 (s, 3H), 4.05-4.1 (m, 1H), 4.2-4.25 (m, 1H), 4.8 (br s, 1H), 6.95 (m, 1H), 7.18 (d, 1H), 7.2 (s, 1H), 7.5 (d, 1H), 7.82 (s, 1H), 8.32 (s, 1H), 9.5 (s, 1H); Mass Spectrum: $M+H^+$ 475 and 477.

[10] The reaction mixture was heated to 40°C for 3 hours rather than to reflux. The product gave the following characterising data: Mass Spectrum: $M+H^+$ 473 and 475.

[11] The reaction mixture was heated to 40°C for 3 hours rather than to reflux. The product gave the following characterising data: NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.0-2.1 (m, 2H), 2.4-2.6 (m, 4H), 2.95 (br s, 2H), 3.72 (s, 3H), 3.88 (s, 3H), 4.0 (m, 2H), 4.12 (m, 1H), 4.9 (d, 1H), 5.6 (m, 2H), 6.88 (d, 1H), 7.1 (d, 1H), 7.15 (s, 1H), 7.4 (d, 1H), 7.75 (s, 1H), 8.25 (s, 1H), 9.43 (s, 1H); Mass Spectrum: $M+H^+$ 471 and 473.

[12] The reaction mixture was heated to 40°C for 3 hours rather than to reflux. The product gave the following characterising data: NMR Spectrum: ($DMSOd_6$) 0.25 (s, 2H), 0.4 (d, 2H), 1.55 (m, 1H), 2.3-2.5 (m, 10H), 3.76 (s, 3H), 3.92 (s, 3H), 4.01 (m, 2H), 4.1-4.2 (m, 1H), 4.9 (m, 1H), 6.9 (m, 1H), 7.1 (s, 1H), 7.2 (s, 1H), 7.45 (d, 1H), 7.8 (s, 1H), 8.3 (s, 1H), 9.5 (s, 1H); Mass Spectrum: $M+H^+$ 514 and 516.

[13] The reaction mixture was heated to 40°C for 3 hours rather than to reflux. The product gave the following characterising data: NMR Spectrum: ($DMSOd_6$) 2.3-2.6 (m, 10H), 2.95 (d, 2H), 3.8 (s, 3H), 3.95 (s, 3H), 4.05 (d, 2H), 4.18 (m, 1H), 4.9 (s, 1H), 5.1-5.2 (m, 2H), 5.8 (m, 1H), 6.92 (d, 1H), 7.15 (s, 1H), 7.2 (s, 1H), 7.5 (d, 1H), 7.82 (s, 1H), 8.35 (s, 1H), 9.5 (s, 1H); Mass Spectrum: $M+H^+$ 514 and 516.

Example 9 4-(2-chloro-5-methoxyanilino)-7-(2-isobutyryloxy-3-pyrrolidin-1-ylpropoxy)-6-methoxyquinazoline dihydrochloride salt

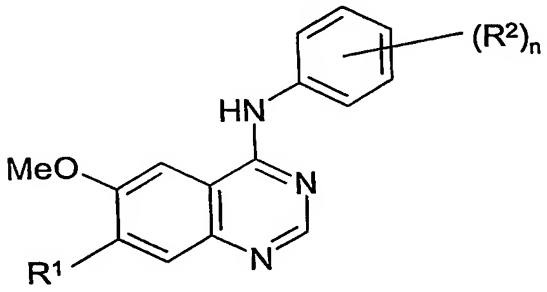
Isobutyric acid (0.02 g) was added to a mixture of 4-(2-chloro-5-methoxyanilino)-7-(2-hydroxy-3-pyrrolidin-1-ylpropoxy)-6-methoxyquinazoline (0.1 g), 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide hydrochloride (0.063 g), 4-dimethylaminopyridine (0.003 g) and methylene chloride (3 ml) and the mixture was stirred at ambient temperature for 16 hours. The mixture was partitioned between ethyl acetate and a 5% aqueous sodium bicarbonate solution. The organic phase was washed with water and with brine, dried over magnesium sulphate, and evaporated. The residue was purified by column chromatography on silica using increasingly polar solvent mixtures of methylene chloride and methanol as eluent. The material so obtained was triturated under a 6M solution of hydrogen chloride in diethyl ether. There was thus obtained the title compound (0.08 g); NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 1.15 (t, 6H), 1.95 (m, 2H), 2.05 (m, 2H), 2.7 (m, 1H), 3.2 (m, 2H), 3.65 (m, 4H), 3.8 (s, 3H), 4.0 (s, 3H), 4.45 (m, 2H), 5.65 (m, 1H), 7.1 (m, 1H),

7.2 (d, 1H), 7.45 (s, 1H), 7.6 (d, 1H), 8.25 (s, 1H), 8.85 (s, 1H), Mass Spectrum: $[M-H]^-$ 527 and 529.

Example 10

Using an analogous procedure to that described in Example 9, the appropriate 7-(2-hydroxypropoxy)quinazoline was reacted with the appropriate carboxylic acid to give the compounds described in Table IV. Unless otherwise stated, each compound described in Table IV was obtained as the dihydrochloride salt.

Table IV



Compound No. & Note	R^1	$(R^2)_n$
[1]	2-(3-methylbutyryloxy)-3-pyrrolidin-1-ylpropoxy	2-chloro-5-methoxy
[2]	2-cyclohexylcarbonyloxy-3-pyrrolidin-1-ylpropoxy	2-chloro-5-methoxy
[3]	2-cyclopentylcarbonyloxy-3-pyrrolidin-1-ylpropoxy	2-chloro-5-methoxy
[4]	2-cyclobutylcarbonyloxy-3-pyrrolidin-1-ylpropoxy	2-chloro-5-methoxy

Notes

[1] The product gave the following characterising data: NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 1.9 (m, 6H), 2.0 (m, 5H), 2.35 (m, 2H), 3.2 (m, 2H), 3.65 (m, 4H), 3.8 (s, 3H), 4.0 (s, 3H), 4.5 (m, 2H), 5.65 (m, 1H), 7.1 (m, 1H), 7.2 (d, 1H), 7.45 (s, 1H), 7.6 (d, 1H), 8.25 (s, 1H), 8.85 (s, 1H); Mass Spectrum: $M+H^+$ 541 and 543.

[2] The product gave the following characterising data: NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 1.2-2.1 (m, 15H), 3.2 (m, 2H), 3.6 (m, 4H), 3.7 (s, 3H), 4.0 (s, 3H), 4.45 (m, 2H), 5.6 (m, 1H), 7.1 (m, 1H), 7.2 (d, 1H), 7. 5 (s, 1H), 7.6 (d, 1H), 8.25 (s, 1H), 8.85 (s, 1H); Mass Spectrum: $M+H^+$ 569 and 571.

[3] The product gave the following characterising data: NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 1.55-2.1 (m, 12 H), 2.9 (m, 1H), 3.2 (m, 2H), 3.65 (m, 4H), 3.8 (s, 3H), 4.0 (s, 3H), 4.4 (m, 1H), 4.5 (m, 1H), 5.6 (m, 1H), 7.1 (m, 1H), 7.2 (d, 1H), 7.45 (s, 1H), 7.6 (d, 1H), 8.2 (s, 1H), 8.85 (s, 1H); Mass Spectrum: $M+H^+$ 555 and 557.

[4] The product gave the following characterising data: NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 1.8-2.3 (m, 11H), 3.1-3.25 (m, 2H), 3.65 (m, 4H), 3.8 (s, 3H), 4.0 (s, 3H), 4.4 (m, 1H), 4.5 (m, 1H), 5.65 (m, 1H), 7.1 (m, 1H), 7.2 (d, 1H), 7.45 (s, 1H), 7.6 (d, 1H), 8.25 (s, 1H), 8.85 (s, 1H); Mass Spectrum: $M+H^+$ 541 and 543.

Example 11 4-(2-bromo-5-methoxyanilino)-7-(2-hydroxy-3-pyrrolidin-1-ylpropoxy)-6-methoxyquinazoline dihydrochloride salt

A mixture of 7-(2-acetoxy-3-pyrrolidin-1-ylpropoxy)-4-(2-bromo-5-methoxyanilino)-6-methoxyquinazoline dihydrochloride (0.123 g) and a saturated methanolic ammonia solution (3 ml) was stirred at ambient temperature for 16 hours. The mixture was evaporated and the residue was purified by column chromatography on silica (Isolute sorbent from International Sorbent Technology Ltd, ref 9470-0100) using a 19:1 mixture of methylene chloride and methanol as eluent. The material so obtained was dissolved in methylene chloride and a 6M solution of hydrogen chloride in isopropanol (0.3 ml) was added. The mixture was diluted with diethyl ether (10 ml) and the resultant solid was collected, washed with diethyl ether and dried under vacuum. There was thus obtained the title compound (0.115 g); NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 1.9 (m, 2H), 2.05 (m, 2H), 3.15 (m, 2H), 3.4 (m, 2H), 3.65 (m, 2H), 3.8 (s, 3H), 4.05 (s, 3H), 4.25 (d, 2H), 4.4 (m, 1H), 7.05 (m, 1H), 7.2 (d, 1H), 7.45 (s, 1H), 7.7 (d, 1H), 8.25 (s, 1H), 8.85 (s, 1H); Mass Spectrum: $M+H^+$ 503 and 505.

The 7-(2-acetoxy-3-pyrrolidin-1-ylpropoxy)-4-(2-bromo-5-methoxyanilino)-6-methoxyquinazoline dihydrochloride used as a starting material was prepared as follows :-

7-(2,3-Epoxypropoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one was reacted with pyrrolidine using an analogous procedure to that described in the second paragraph of the portion of Note [6] in Example 4 above that is concerned with the preparation of starting materials. There was thus obtained 7-(2-hydroxy-3-pyrrolidin-1-ylpropoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one.

The material so obtained was taken through an analogous sequence of reactions to those described in the third to fifth paragraphs of the portion of Note [6] in Example 4 above

that is concerned with the preparation of starting materials. There was thus obtained 7-(2-acetoxy-3-pyrrolidin-1-ylpropoxy)-4-chloro-6-methoxyquinazoline; NMR Spectrum: ($CDCl_3$ and CD_3CO_2D) 2.05 (s, 4H), 2.15 (s, 3H), 3.45 (br s, 4H), 3.65 (m, 2H), 4.05 (s, 3H), 4.4 (d, 2H), 5.65 (m, 1H), 7.4 (s, 1H), 7.55 (s, 1H), 8.9 (s, 1H).

The material so obtained was reacted with 2-bromo-5-methoxyaniline using an analogous procedure to that described in Example 3. There was thus obtained 7-(2-acetoxy-3-pyrrolidin-1-ylpropoxy)-4-(2-bromo-5-methoxyanilino)-6-methoxyquinazoline dihydrochloride salt; Mass Spectrum: $M+H^+$ 545 and 547.

Example 12 4-(2-bromo-5-methoxyanilino)-7-[2-hydroxy-3-(N-isopropyl-N-methylamino)propoxy]-6-methoxyquinazoline dihydrochloride salt

Using an analogous procedure to that described in Example 11, 7-[2-acetoxy-3-(N-isopropyl-N-methylamino)propoxy]-4-(2-bromo-5-methoxyanilino)-6-methoxyquinazoline dihydrochloride was reacted with a saturated methanolic ammonia solution to give the title compound; Mass Spectrum: $M+H^+$ 505 and 507.

The 7-[2-acetoxy-3-(N-isopropyl-N-methylamino)propoxy]-4-(2-bromo-5-methoxyanilino)-6-methoxyquinazoline dihydrochloride used as a starting material was prepared as follows :-

7-(2,3-Epoxypropoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one was reacted with N-isopropyl-N-methylamine using an analogous procedure to that described in the second paragraph of the portion of Note [6] in Example 4 above that is concerned with the preparation of starting materials. There was thus obtained 7-[2-hydroxy-3-(N-isopropyl-N-methylamino)propoxy]-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one.

The material so obtained was taken through an analogous sequence of reactions to those described in the third to fifth paragraphs of the portion of Note [6] in Example 4 above that is concerned with the preparation of starting materials. There was thus obtained 7-[2-acetoxy-3-(N-isopropyl-N-methylamino)propoxy]-4-chloro-6-methoxyquinazoline; NMR Spectrum: ($CDCl_3$) 1.0 (d, 6H), 2.1 (s, 3H), 2.3 (s, 3H), 2.6 (m, 1H), 2.75 (m, 1H), 2.85 (m, 1H), 4.05 (s, 3H), 4.35 (m, 1H), 4.45 (m, 1H), 5.35 (m, 1H), 7.25 (s, 1H), 7.4 (s, 1H), 8.85 (s, 1H).

The material so obtained was reacted with 2-bromo-5-methoxyaniline using an analogous procedure to that described in Example 3. There was thus obtained 7-[2-acetoxy-

3-(N-isopropyl-N-methylamino)propoxy]-4-(2-bromo-5-methoxyanilino)-6-methoxyquinazoline dihydrochloride salt; Mass Spectrum: $M+H^+$ 547 and 549.

Example 13 4-(2-chloro-5-methoxyanilino)-7-[(2R)-(2-hydroxy-3-morpholinopropoxy]-6-methoxyquinazoline dihydrochloride salt

A mixture of 4-(2-chloro-5-methoxyanilino)-7-[(2R)-2,3-epoxypropoxy]-6-methoxyquinazoline (0.1 g), morpholine (2.5 equivalents), chloroform (2.5 ml) and ethanol (2.5 ml) was stirred and heated to 40°C for 8 hours. The solvent was evaporated. Methylene chloride (5 ml) and a polystyrene isocyanate resin (0.3 g; loading: 1 mmol/g; prepared according to the procedure disclosed in J. Amer. Chem. Soc., 1997, 119, 4882) was added and the mixture was stirred at ambient temperature for 1.5 hours. The mixture was filtered and the filtrate was evaporated. The crude product so obtained was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and a saturated methanolic ammonia solution as eluent. There was thus obtained the title compound; NMR Spectrum: ($DMSOd_6$) 2.4-2.6 (m, 6H), 3.6 (m, 4H), 3.8 (s, 3H), 3.95 (s, 3H), 4.05 (d, 2H), 4.2 (m, 1H), 4.95 (d, 1H), 6.9 (m, 1H), 7.15 (d, 1H), 7.2 (s, 1H), 7.5 (d, 1H), 7.8 (s, 1H), 8.3 (s, 1H), 9.5 (s, 1H); Mass Spectrum: $M+H^+$ 475 and 477.

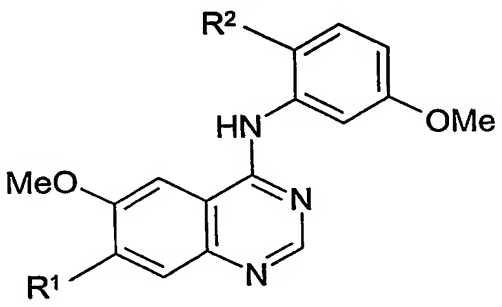
The 4-(2-chloro-5-methoxyanilino)-7-[(2R)-2,3-epoxypropoxy]-6-methoxyquinazoline used as a starting material was prepared as follows :-

(2R)-(-)-Glycidyl tosylate (3.6 g) was added to a mixture of 4-(2-chloro-5-methoxyanilino)-7-hydroxy-6-methoxyquinazoline (4.8 g), potassium carbonate (8.5 g) and DMF (60 ml) and the mixture was stirred and heated to 40°C for 4 hours. The resultant mixture was filtered and the filtrate was evaporated. The residue was partitioned between methylene chloride and water. The organic phase was washed in turn with a 5% aqueous ammonium hydroxide solution, with water and with brine, dried over magnesium sulphate and evaporated. The material so obtained was washed with a 4:1 mixture of petroleum ether and diethyl ether and dried under vacuum. There was thus obtained 4-(2-chloro-5-methoxyanilino)-7-[(2R)-2,3-epoxypropoxy]-6-methoxyquinazoline as a solid (3.1 g); NMR Spectrum: ($DMSOd_6$) 2.8 (m, 1H), 2.9 (m, 1H), 3.45 (m, 1H), 3.8 (s, 3H), 3.95 (s, 3H), 4.0 (m, 1H), 4.55 (m, 1H), 6.9 (m, 1H), 7.15 (d, 1H), 7.2 (s, 1H), 7.55 (d, 1H), 7.85 (s, 1H), 8.3 (s, 1H), 9.5 (br s, 1H).

Example 14

Using an analogous procedure to that described in Example 13, the appropriate 7-(2,3-epoxypropoxy)quinazoline was reacted with the appropriate heterocyclic compound or amine to give the compounds described in Table V. In each case, the reaction product was dissolved in a 9:1 mixture of methylene chloride and methanol and a 2.2M hydrogen chloride solution in diethyl ether was added. Each precipitate was isolated and dried under vacuum to give the desired products as dihydrochloride salts.

Table V



Compound No. & Note	R^1	R^2
[1]	(2R)-3-(N-allyl-N-cyclopentylamino)-2-hydroxypropoxy	chloro
[2]	(2R)-3-(N-allyl-N-methylamino)-2-hydroxypropoxy	chloro
[3]	(2R)-2-hydroxy-3-(N-isobutyl-N-methylamino)propoxy	bromo
[4]	(2R)-2-hydroxy-3-piperidinopropoxy	bromo

Notes

[1] The product gave the following characterising data: NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 1.5-1.65 (m, 2H), 1.68-1.96 (m, 4H), 2.0-2.17 (m, 2H), 3.25-3.43 (m, 2H), 3.75 (m, 1H), 3.82 (s, 3H), 3.92 (d, 2H), 3.95 (m, 1H), 4.0 (s, 3H), 4.2-4.35 (m, 2H), 4.43-4.58 (m, 1H), 5.53-5.73 (m, 2H), 6.02-6.18 (m, 1H), 7.1 (m, 1H), 7.2 (d, 1H), 7.45 (s, 1H), 7.6 (d, 1H), 8.25 (s, 1H), 8.85 (s, 1H); Mass Spectrum: $M\text{-}H^-$ 511 and 513.

[2] The product gave the following characterising data: NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.85 (br s, 3H), 3.19-3.44 (m, 2H), 3.81 (s, 3H), 3.77-3.97 (m, 2H), 4.03 (s, 3H), 4.2-4.3 (m, 2H), 4.44-4.56 (m, 1H), 5.51-5.64 (m, 2H), 5.95-6.08 (m, 1H), 7.08 (m, 1H), 7.2

(d, 1H), 7.5 (br s, 1H), 7.57 (d, 1H), 8.3 (br s, 1H), 8.84 (s, 1H); Mass Spectrum: M-H$^-$ 457 and 459.

[3] The product gave the following characterising data: NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 0.93-1.1 (m, 6H), 2.06-2.22 (m, 1H), 2.9 (s, 3H), 2.9-3.03 (m, 1H), 3.09-3.48 (m, 3H), 3.81 (s, 3H), 4.03 (s, 3H), 4.2-4.31 (m, 2H), 4.46-4.58 (m, 1H), 7.02 (m, 1H), 1.19 (d, 1H), 7.49 (s, 1H), 7.72 (d, 1H), 8.26 (s, 1H), 8.84 (s, 1H); Mass Spectrum: M-H$^-$ 517 and 519.

The 4-(2-bromo-5-methoxyanilino)-7-[(2R)-2,3-epoxypropoxy]-6-methoxyquinazoline used as a starting material was prepared as follows :-

A 1M solution in THF of the sodium salt of 1,1,1,3,3,3-hexamethyldisilazane (82.4 ml) was added dropwise to a mixture of 2-bromo-5-methoxyaniline (16.7 g) and DMF (200 ml) and the reaction mixture was stirred at ambient temperature for a further 30 minutes. A solution of 7-benzyloxy-4-chloro-6-methoxyquinazoline (11.8 g) in DMF (250 ml) was added and the reaction mixture was at ambient temperature for 20 minutes. The mixture was concentrated by evaporation of about half of the DMF. The residue was partitioned between methylene chloride and water . The organic phase was dried over magnesium sulphate and evaporated. The resultant solid was washed with a 1:1 mixture of petroleum ether and diethyl ether and dried overnight under vacuum. There was thus obtained 4-(2-bromo-5-methoxyanilino)-7-benzyloxy-6-methoxyquinazoline (13.1 g); NMR Spectrum: ($DMSOd_6$) 3.8 (s, 3H), 3.95 (s, 3H), 5.3 (s, 2H), 6.85 (m, 1H), 7.15 (d, 1H), 7.3 (s, 1H), 7.35-7.55 (m, 5H), 7.6 (d, 1H), 7.85 (s, 1H), 8.3 (s, 1H), 9.5 (br s, 1H).

A mixture of the material so obtained and trifluoroacetic acid (130 ml) was stirred and heated to reflux for 5 hours. The mixture was evaporated, water was added and the mixture was neutralised by the addition of a saturated aqueous sodium bicarbonate solution. The resultant solid was dried under vacuum to give 4-(2-bromo-5-methoxyanilino)-7-hydroxy-6-methoxyquinazoline (11 g); Mass Spectrum: M-H$^-$ 374 and 376.

(2R)-(-)-Glycidyl tosylate (3.6 g) was added to a mixture of 4-(2-bromo-5-methoxyanilino)-7-hydroxy-6-methoxyquinazoline (5 g), potassium carbonate (7.3 g) and DMF (60 ml) and the mixture was stirred and heated to 40°C for 4 hours. The resultant mixture was filtered and the filtrate was evaporated. The residue was partitioned between methylene chloride and water. The organic phase was washed in turn with a 5% aqueous ammonium hydroxide solution, with water and with brine, dried over magnesium sulphate and evaporated. The material so obtained was washed with a 4:1 mixture of petroleum ether and diethyl ether and dried under vacuum. There was thus obtained 4-(2-bromo-

5-methoxyanilino)-7-[(2R)-2,3-epoxypropoxy]-6-methoxyquinazoline as a solid (3.6 g); NMR Spectrum: ($DMSOd_6$) 2.8 (m, 1H), 2.9 (m, 1H), 3.45 (m, 1H), 3.8 (s, 3H), 3.95 (s, 3H), 4.05 (m, 1H), 4.55 (m, 1H), 6.9 (m, 1H), 7.15 (d, 1H), 7.2 (s, 1H), 7.6 (d, 1H), 7.85 (s, 1H), 8.3 (s, 1H), 9.5 (br s, 1H); Mass Spectrum: $M+H^+$ 432 and 434.

[4] The product gave the following characterising data: NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 1.33-1.52 (m, 1H), 1.64-1.97 (m, 5H), 2.93-3.14 (m, 2H), 3.2-3.4 (m, 2H), 3.47-3.64 (m, 2H), 3.82 (s, 3H), 4.04 (s, 3H), 4.26 (s, 2H), 4.46-4.59 (m, 1H), 7.03 (m, 1H), 7.21 (d, 1H), 7.46 (s, 1H), 7.73 (d, 1H), 8.21 (s, 1H), 8.56 (s, 1H); Mass Spectrum: $M-H^-$ 515 and 517.

Src Inhibitors described within International Patent Application PCT/GB 02/02124

Example 1 4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline dihydrochloride salt

A mixture of 4-chloro-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline (0.1 g), 2,4-dichloro-5-methoxyaniline (0.066 g), a 6M solution of hydrogen chloride in isopropanol (0.1 ml) and isopropanol (4 ml) was stirred and heated to 80°C for 2 hours. The mixture was cooled to ambient temperature and the precipitate was isolated, washed in turn with isopropanol and diethyl ether and dried under vacuum. There was thus obtained the title compound (0.106 g); NMR Spectrum: ($DMSOd_6$) 1.6-17.5 (m, 2H), 2.02 (d, 2H), 2.15 (br s, 1H), 2.75 (d, 3H), 3.0 (m, 2H), 3.15-3.3 (m, 2H), 3.9 (s, 3H), 4.05 (s, 3H), 4.1 (d, 2H), 7.42 (s, 1H), 7.5 (s, 1H), 7.82 (s, 1H), 8.32 (s, 1H), 8.8 (s, 1H), 10.35 (br s, 1H); Mass Spectrum: $M+H^+$ 477 and 479.

The 4-chloro-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline used as a starting material was prepared as follows :-

A solution of di-tert-butyl dicarbonate (41.7 g) in ethyl acetate (75 ml) was added dropwise to a stirred solution of ethyl piperidine-4-carboxylate (30 g) in ethyl acetate (150 ml) which had been cooled to 0 to 5°C in an ice-bath. The resultant mixture was stirred at ambient temperature for 48 hours. The mixture was poured into water (300 ml). The organic layer was separated, washed in turn with water (200 ml), 0.1N aqueous hydrochloric acid solution (200 ml), a saturated aqueous sodium bicarbonate solution (200 ml) and brine (200 ml), dried over magnesium sulphate and evaporated. There was thus obtained ethyl N-tert-butoxycarbonylpiperidine-4-carboxylate (48 g); NMR Spectrum: ($CDCl_3$) 1.25 (t, 3H),

1.45 (s, 9H), 1.55-1.7 (m, 2H), 1.8-2.0 (d, 2H), 2.35-2.5 (m, 1H), 2.7-2.95 (t, 2H), 3.9-4.1 (br s, 2H), 4.15 (q, 2H).

A solution of the material so obtained in THF (180 ml) was cooled at 0°C and lithium aluminium hydride (1M solution in THF; 133 ml) was added dropwise. The mixture was stirred at 0°C for 2 hours. Water (30 ml) and 2N aqueous sodium hydroxide solution (10 ml) were added in turn and the mixture was stirred for 15 minutes. The resultant mixture was filtered through diatomaceous earth and the solids were washed with ethyl acetate. The filtrate was washed in turn with water and with brine, dried over magnesium sulphate and evaporated. There was thus obtained N-tert-butoxycarbonyl-4-hydroxymethylpiperidine (36.3 g); NMR Spectrum: ($CDCl_3$) 1.05-1.2 (m, 2H), 1.35-1.55 (m, 10H), 1.6-1.8 (m, 2H), 2.6-2.8 (t, 2H), 3.4-3.6 (t, 2H), 4.0-4.2 (br s, 2H).

1,4-Diazabicyclo[2.2.2]octane (42.4 g) was added to a solution of N-tert-butoxycarbonyl-4-hydroxymethylpiperidine (52.5 g) in tert-butyl methyl ether (525 ml) and the mixture was stirred at ambient temperature for 15 minutes. The mixture was then cooled in an ice-bath to 5°C and a solution of 4-toluenesulphonyl chloride (62.8 g) in tert-butyl methyl ether (525 ml) was added dropwise over 2 hours while maintaining the reaction temperature at approximately 0°C. The resultant mixture was allowed to warm to ambient temperature and was stirred for 1 hour. Petroleum ether (b.p. 60-80°C, 1L) was added and the precipitate was removed by filtration. The filtrate was evaporated to give a solid residue which was dissolved in diethyl ether. The organic solution was washed in turn with 0.5N aqueous hydrochloric acid solution, water, a saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and evaporated. There was thus obtained N-tert-butoxycarbonyl-4-(4-toluenesulphonyloxymethyl)piperidine (76.7 g); NMR Spectrum: ($CDCl_3$) 1.0-1.2 (m, 2H), 1.45 (s, 9H), 1.65 (d, 2H), 1.75-1.9 (m, 2H), 2.45 (s, 3H), 2.55-2.75 (m, 2H), 3.85 (d, 1H), 4.0-4.2 (br s, 2H), 7.35 (d, 2H), 7.8 (d, 2H).

A portion (40 g) of the material so obtained was added to a suspension of ethyl 4-hydroxy-3-methoxybenzoate (19.6 g) and potassium carbonate (28 g) in DMF (200 ml) and the resultant mixture was stirred and heated to 95°C for 2.5 hours. The mixture was cooled to ambient temperature and partitioned between water and a mixture of ethyl acetate and diethyl ether. The organic layer was washed in turn with water and brine, dried over magnesium sulphate and evaporated. The resulting oil was crystallised from petroleum ether (b.p. 60-80°C) and the suspension was stored overnight at 5°C. The resultant solid was

collected by filtration, washed with petroleum ether and dried under vacuum. There was thus obtained ethyl 4-(N-tert-butoxycarbonylpiperidin-4-ylmethoxy)-3-methoxybenzoate (35 g), m.p. 81-83°C; NMR Spectrum: ($CDCl_3$) 1.2-1.35 (m, 2H), 1.4 (t, 3H), 1.48 (s, 9H), 1.8-1.9 (d, 2H), 2.0-2.15 (m, 2H), 2.75 (t, 2H), 3.9 (d, 2H), 3.95 (s, 3H), 4.05-4.25 (br s, 2H), 4.35 (q, 2H), 6.85 (d, 1H), 7.55 (s, 1H), 7.65 (d, 1H).

The material so obtained was dissolved in formic acid (35 ml), formaldehyde (12M, 37% in water, 35 ml) was added and the mixture was stirred and heated to 95°C for 3 hours. The resultant mixture was evaporated. The residue was dissolved in methylene chloride and hydrogen chloride (3M solution in diethyl ether; 40 ml) was added. The mixture was diluted with diethyl ether and the mixture was triturated until a solid was formed. The solid was collected, washed with diethyl ether and dried under vacuum overnight at 50°C. There was thus obtained ethyl 3-methoxy-4-(N-methylpiperidin-4-ylmethoxy)benzoate (30.6 g); NMR Spectrum: ($DMSOd_6$) 1.29 (t, 3H), 1.5-1.7 (m, 2H), 1.95 (d, 2H), 2.0-2.15 (br s, 1H), 2.72 (s, 3H), 2.9-3.1 (m, 2H), 3.35-3.5 (br s, 2H), 3.85 (s, 3H), 3.9-4.05 (br s, 2H), 4.3 (q, 2H), 7.1 (d, 1H), 7.48 (s, 1H), 7.6 (d, 1H).

The material so obtained was dissolved in methylene chloride (75 ml) and the solution was cooled in an ice-bath to 0-5°C. Trifluoroacetic acid (37.5 ml) was added followed by the dropwise addition over 15 minutes of a solution of fuming nitric acid (24M; 7.42 ml) in methylene chloride (15 ml). The resultant solution was allowed to warm to ambient temperature and was stirred for 2 hours. Volatile materials were evaporated. The residue was dissolved in methylene chloride (50 ml) and the solution was cooled in an ice-bath to 0-5°C. Diethyl ether was added and the resultant precipitate was collected and dried under vacuum at 50°C. The solid was dissolved in methylene chloride (500 ml) and hydrogen chloride (3M solution in diethyl ether; 30 ml) was added followed by diethyl ether (500 ml). The resultant solid was collected and dried under vacuum at 50°C. There was thus obtained ethyl 5-methoxy-4-(N-methylpiperidin-4-ylmethoxy)-2-nitrobenzoate (28.4 g); NMR Spectrum: ($DMSOd_6$) 1.3 (t, 3H), 1.45-1.65 (m, 2H), 1.75-2.1 (m, 3H), 2.75 (s, 3H), 2.9-3.05 (m, 2H), 3.4-3.5 (d, 2H), 3.95 (s, 3H), 4.05 (d, 2H), 4.3 (q, 2H), 7.32 (s, 1H), 7.66 (s, 1H).

A mixture of a portion (3.89 g) of the material so obtained, 10% platinum-on-activated carbon (50% wet, 0.389 g) and methanol (80 ml) was stirred under 1.8 atmospheres pressure of hydrogen until uptake of hydrogen ceased. The mixture was filtered and the filtrate was evaporated. The residue was dissolved in water (30 ml) and basified to pH10 by the addition of a saturated aqueous sodium bicarbonate solution. The mixture was diluted with a 1:1

mixture of ethyl acetate and diethyl ether and the organic layer was separated. The aqueous layer was further extracted with a 1:1 mixture of ethyl acetate and diethyl ether and the organic extracts were combined, washed in turn with water and brine, dried over magnesium sulphate and evaporated. The residue was triturated under a mixture of petroleum ether (b.p. 60-80°C) and diethyl ether. The solid so obtained was isolated, washed with petroleum ether and dried under vacuum at 60°C. There was thus obtained ethyl 2-amino-5-methoxy-4-(N-methylpiperidin-4-ylmethoxy)benzoate (2.58 g), m.p. 111-112°C; NMR Spectrum: ($CDCl_3$) 1.35 (t, 3H), 1.4-1.5 (m, 2H), 1.85 (m, 3H), 1.95 (t, 2H), 2.29 (s, 3H), 2.9 (d, 2H), 3.8 (s, 3H), 3.85 (d, 2H), 4.3 (q, 2H), 5.55 (br s, 2H), 6.13 (s, 1H), 7.33 (s, 1H).

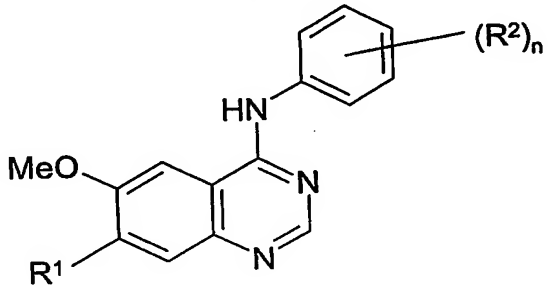
A mixture of ethyl 2-amino-5-methoxy-4-(N-methylpiperidin-4-ylmethoxy)benzoate (16.1 g), formamidine acetic acid salt (5.2 g) and 2-methoxyethanol (160 ml) was stirred and heated at 115°C for 2 hours. Further formamidine acetic acid salt (10.4 g) was added in portions every 30 minutes during 4 hours and heating was continued for 30 minutes after the last addition. The resultant mixture was evaporated. The solid residue was stirred under a mixture of methylene chloride (50ml) and ethanol (100ml). The precipitate was removed by filtration and the filtrate was concentrated to a final volume of 100ml. The resultant suspension was cooled to 5°C. The solid so obtained was collected, washed with cold ethanol and with diethyl ether and dried under vacuum at 60°C. There was thus obtained 6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)-3,4-dihydroquinazolin-4-one (12.7 g); NMR Spectrum: ($DMSOd_6$) 1.25-1.4 (m, 2H), 1.75 (d, 2H), 1.9 (t, 1H), 1.9 (s, 3H), 2.16 (s, 2H), 2.8 (d, 2H), 3.9 (s, 3H), 4.0 (d, 2H), 7.11 (s, 1H), 7.44 (s, 1H), 7.97 (s, 1H).

A mixture of a portion (2.8 g) of the material so obtained, thionyl chloride (28 ml) and DMF (0.28 ml) was heated to reflux for 1 hour. The mixture was evaporated and the precipitate was triturated under diethyl ether. The resultant solid was isolated and washed with diethyl ether. The solid was then dissolved in methylene chloride and the solution was washed with a saturated aqueous sodium bicarbonate solution. The organic layer was washed in turn with water and brine, dried over magnesium sulphate and evaporated. There was thus obtained 4-chloro-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline (2.9 g); NMR Spectrum: ($DMSOd_6$) 1.3-1.5 (m, 2H), 1.75-1.9 (m, 4H), 2.0 (t, 1H), 2.25 (s, 3H), 2.85 (d, 2H), 4.02 (s, 3H), 4.12 (d, 2H), 7.41 (s, 1H), 7.46 (s, 1H), 8.9 (s, 1H).

Example 2

Using an analogous procedure to that described in Example 1, the appropriate 4-chloroquinazoline was reacted with the appropriate aniline to give the compounds described in Table I. Unless otherwise stated, each compound described in Table I was obtained as a dihydrochloride salt.

Table I



Compound No. & Note	R^1	$(R^2)_n$
[1]	piperidin-4-ylmethoxy	2,4-dichloro-5-methoxy
[2]	2-(N-methylpiperidin-4-yl)ethoxy	2,4-dichloro-5-methoxy
[3]	2-piperidin-4-ylethoxy	2,4-dichloro-5-methoxy
[4]	3-piperazin-1-ylpropoxy	2,4-dichloro-5-methoxy
[5]	3-morpholinopropoxy	2,4-dichloro-5-methoxy
[6]	2-acetoxy-3-morpholinopropoxy	2,4-dichloro-5-methoxy
[7]	2-acetoxy-3-(N-isopropyl-N-methylamino)propoxy	2,4-dichloro-5-methoxy
[8]	2-acetoxy-3-piperidinopropoxy	2,4-dichloro-5-methoxy
[9]	2-acetoxy-3-pyrrolidin-1-ylpropoxy	2,4-dichloro-5-methoxy
[10]	2-acetoxy-3-(4-cyanomethylpiperazin-1-yl)propoxy	2,4-dichloro-5-methoxy

Notes

[1] 7-(N-tert-Butoxycarbonylpiperidin-4-ylmethoxy)-4-chloro-6-methoxyquinazoline was used as the appropriate 4-chloroquinazoline. The product was obtained as the monohydrochloride salt and gave the following characterising data: NMR Spectrum: ($DMSOd_6$) 1.5-1.7 (m, 2H), 2.0 (d, 2H), 2.15-2.3 (m, 1H), 2.9-3.05 (m, 2H), 3.4-3.5 (m, 2H), 3.9 (s, 3H), 4.06 (s, 3H), 4.11 (d, 2H), 7.43 (s, 1H), 7.48 (s, 1H), 7.83 (s, 1H), 8.34 (s, 1H), 8.80 (s, 1H), 8.7-8.8 (m, 1H), 9.0-9.1 (m, 1H); Mass Spectrum: $M-H^-$ 461 and 463.

The 7-(N-tert-butoxycarbonylpiperidin-4-ylmethoxy)-4-chloro-6-methoxyquinazoline used as a starting material was prepared as follows :-

Sodium hydride (60% suspension in mineral oil, 1.44 g) was added portionwise during 20 minutes to a solution of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (International Patent Application WO 97/22596, Example 1 thereof; 8.46 g) in DMF (70 ml). The mixture was stirred at ambient temperature for 1.5 hours. Chloromethyl pivalate (5.65 g) was added dropwise and the mixture was stirred at ambient temperature for 2 hours. The mixture was diluted with ethyl acetate (100 ml) and poured onto a mixture (400 ml) of ice and water containing 2N aqueous hydrochloric acid (4 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined extracts were washed with brine, dried over magnesium sulphate and evaporated. The residue was triturated under a mixture of diethyl ether and petroleum ether (b.p. 60-80°C) and the resultant solid was collected and dried under vacuum. There was thus obtained 7-benzyloxy-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (10 g); NMR Spectrum: ($DMSOd_6$) 1.11 (s, 9H), 3.89 (s, 3H), 5.3 (s, 2H), 5.9 (s, 2H), 7.27 (s, 1H), 7.35 (m, 1H), 7.47 (t, 2H), 7.49 (d, 2H), 7.51 (s, 1H), 8.34 (s, 1H).

A mixture of a portion (7 g) of the material so obtained, 10% palladium-on-charcoal catalyst (0.7 g), DMF (50 ml), methanol (50 ml), acetic acid (0.7 ml) and ethyl acetate (250 ml) was stirred under an atmosphere pressure of hydrogen for 40 minutes. The catalyst was removed by filtration and the solvent was evaporated. The residue was triturated under diethyl ether and the resultant solid was collected and dried under vacuum. There was thus obtained 7-hydroxy-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (4.36 g); NMR Spectrum: ($DMSOd_6$) 1.1 (s, 9H), 3.89 (s, 3H), 5.89 (s, 2H), 7.0 (s, 1H), 7.48 (s, 1H), 8.5 (s, 1H).

Using an analogous procedure to that described in the fourth paragraph of the portion of Example 1 that is concerned with the preparation of starting materials, 7-hydroxy-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one was reacted with N-tert-butoxycarbonyl-4-(4-toluenesulphonyloxymethyl)piperidine to give 7-(N-tert-butoxycarbonylpiperidin-4-ylmethoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one.

A mixture of 7-(N-tert-butoxycarbonylpiperidin-4-ylmethoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (6 g) and a saturated methanolic ammonia solution (100ml) was stirred at ambient temperature for 16 hours. The resultant mixture was

evaporated and the residue was triturated under diethyl ether. The solid so obtained was isolated, washed with a 49:1 mixture of diethyl ether and methylene chloride and dried under vacuum. There was thus obtained 7-(N-tert-butoxycarbonylpiperidin-4-ylmethoxy)-6-methoxy-3,4-dihydroquinazolin-4-one (3.3 g); NMR Spectrum: ($DMSOd_6$) 1.12-1.3 (m, 2H), 1.42 (s, 9H), 1.8 (d, 2H), 2.02 (m, 1H), 2.7-2.9 (m, 2H), 3.9 (s, 3H), 4.02 (d, 4H), 7.15 (s, 1H), 7.45 (s, 1H), 8.0 (s, 1H).

A mixture of a portion (0.2 g) of the material so obtained, carbon tetrachloride (0.15 ml), triphenylphosphine (0.25 g) and 1,2-dichloroethane (10 ml) was stirred and heated to 70°C for 2 hours. The mixture was evaporated and the residue was purified by column chromatography on silica using a 5:4:1 mixture of methylene chloride, ethyl acetate and methanol as eluent. There was thus obtained 7-(N-tert-butoxycarbonylpiperidin-4-ylmethoxy)-4-chloro-6-methoxyquinazoline (0.07 g); NMR Spectrum: ($DMSOd_6$) 1.15-1.3 (m, 2H), 1.45 (s, 9H), 1.8 (d, 2H), 2.08 (m, 1H), 2.7-2.9 (m, 2H), 4.02 (m, 5H), 4.12 (d, 2H), 7.42 (s, 1H), 7.5 (s, 1H), 8.9 (s, 1H); Mass Spectrum: $M+H^+$ 408.

[2] The reaction product so obtained was mixed with methylene chloride (5 ml) and a saturated methanolic ammonia solution (0.5 ml) was added. The mixture was stirred at ambient temperature for 10 minutes. The mixture was filtered and the filtrate was evaporated. The residue was dissolved in diethyl ether and a 3M solution of hydrogen chloride in diethyl ether (0.5 ml) was added. The mixture was evaporated and the residue was triturated under diethyl ether. The resultant solid was isolated, washed with diethyl ether and dried under vacuum. There was thus obtained the dihydrochloride salt of the required compound which gave the following characterising data: NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 1.4-1.55 (m, 2H), 1.7-1.9 (m, 3H), 2.0 (d, 2H), 2.75 (s, 3H), 2.95 (m, 2H), 3.42 (d, 2H), 3.85 (s, 3H), 3.98 (s, 3H), 4.25 (m, 2H), 7.32 (s, 1H), 7.38 (s, 1H), 7.7 (s, 1H), 8.12 (s, 1H), 8.8 (s, 1H); Mass Spectrum: $M+H^+$ 491 and 493.

The 4-chloro-6-methoxy-7-[2-(N-methylpiperidin-4-yl)ethoxy]quinazoline used as a starting material is described in International Patent Application WO 00/47212 (example 241 thereof).

[3] 7-[2-(N-tert-Butoxycarbonylpiperidin-4-yl)ethoxy]-4-chloro-6-methoxyquinazoline was used as the appropriate 4-chloroquinazoline. The product was obtained as the monohydrochloride salt and gave the following characterising data: NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 1.4-1.5 (m, 2H), 1.85 (m, 3H), 1.95 (d, 2H), 2.95 (m, 2H), 3.32 (d,

2H), 3.91 (s, 3H), 4.03 (s, 3H), 4.3 (m, 2H), 7.4 (s, 1H), 7.45 (s, 1H), 7.8 (s, 1H), 8.16 (s, 1H), 8.87 (s, 1H); Mass Spectrum: M-H$^-$ 475 and 477.

The 7-[2-(N-tert-butoxycarbonylpiperidin-4-yl)ethoxy]-4-chloro-6-methoxyquinazoline used as a starting material was obtained as follows :-

A mixture of 7-hydroxy-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (2 g), N-tert-butoxycarbonyl-4-[2-(4-toluenesulphonyloxy)ethyl]piperidine (2.84 g), potassium carbonate (1.8 g) and DMF (20 ml) was stirred and heated to 95°C for 2.5 hours. The resultant mixture was cooled to ambient temperature and poured onto a mixture of ice and water. The mixture was extracted with methylene chloride. The organic layer was washed with brine, dried over magnesium sulphate and evaporated. There was thus obtained 7-[2-(N-tert-butoxycarbonylpiperidin-4-yl)ethoxy]-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (2 g); NMR Spectrum: (DMSOd_6) 1.0-1.15 (m, 2H), 1.15 (s, 9H), 1.4 (s, 9H), 1.6-1.8 (m, 3H), 2.6-2.8 (m, 2H), 3.92 (s, 3H), 3.9-4.0 (m, 2H), 4.2 (m, 2H), 5.92 (s, 2H), 7.2 (s, 1H), 7.5 (s, 1H), 8.3 (s, 1H).

Using an analogous procedure to that described in the fourth paragraph of the portion of Note [1] immediately above that is concerned with the preparation of starting materials, 7-[2-(N-tert-butoxycarbonylpiperidin-4-yl)ethoxy]-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (2 g) was treated with a saturated methanolic ammonia solution to give 7-[2-(N-tert-butoxycarbonylpiperidin-4-yl)ethoxy]-6-methoxy-3,4-dihydroquinazolin-4-one (1.3 g); NMR Spectrum: (DMSOd_6) 1.0-1.15 (m, 2H), 1.4 (s, 9H), 1.6-1.8 (m, 3H), 2.6-2.8 (m, 2H), 3.3-3.5 (m, 2H), 3.9 (s, 3H), 3.9-4.0 (m, 2H), 4.18 (m, 2H), 7.15 (s, 1H), 7.45 (s, 1H), 8.0 (s, 1H); Mass Spectrum: M+H$^+$ 404.

Using an analogous procedure to that described in the fifth paragraph of the portion of Note [1] immediately above that is concerned with the preparation of starting materials, 7-[2-(N-tert-butoxycarbonylpiperidin-4-yl)ethoxy]-6-methoxy-3,4-dihydroquinazolin-4-one (0.2 g) was reacted with carbon tetrachloride and triphenylphosphine to give 7-[2-(N-tert-butoxycarbonylpiperidin-4-yl)ethoxy]-4-chloro-6-methoxyquinazoline (0.03 g); NMR Spectrum: (DMSOd_6) 1.0-1.2 (m, 2H), 1.4 (s, 9H), 1.6-1.8 (m, 5H), 2.6-2.8 (m, 2H), 3.92 (d, 2H), 4.0 (s, 3H), 4.3 (m, 2H), 7.4 (s, 1H), 7.5 (s, 1H), 8.9 (s, 1H).

The N-tert-butoxycarbonyl-4-[2-(4-toluenesulphonyloxy)ethyl]piperidine used as a starting material was prepared by the reaction of 4-toluenesulphonyl chloride with N-tert-butoxycarbonyl-4-(2-hydroxyethyl)piperidine (International Patent Application WO 00/47212, in example 126 thereof) using an analogous procedure to that described in the

third paragraph of the portion of Example 1 that is concerned with the preparation of starting materials.

[4] 7-[3-(4-tert-Butoxycarbonylpiperazin-1-yl)propoxy]-4-chloro-6-methoxyquinazoline was used as the appropriate 4-chloroquinazoline. The product gave the following characterising data: NMR Spectrum: ($DMSOd_6$) 2.3-2.4 (m, 2H), 3.3-3.5 (m, 10H), 3.88 (s, 3H), 4.02 (s, 3H), 4.35 (m, 2H), 7.42 (s, 1H), 7.45 (s, 1H), 7.82 (s, 1H), 8.32 (s, 1H), 8.8 (s, 1H); Mass Spectrum: $M+H^+$ 492 and 494.

The 7-[3-(4-tert-butoxycarbonylpiperazin-1-yl)propoxy]-4-chloro-6-methoxyquinazoline used as a starting material was obtained as follows :-

A mixture of 7-(3-bromopropoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (International Patent Application WO 00/47212, example 67; 4.5 g), tert-butyl piperazine-1-carboxylate (2.16 g), sodium iodide (0.079 g), potassium carbonate (2.9 g) and acetonitrile (150 ml) was stirred and heated to reflux for 8 hours. The resultant mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography on silica using a 19:1 mixture of methylene chloride and methanol as eluent. There was thus obtained 7-[3-(4-tert-butoxycarbonylpiperazin-1-yl)propoxy]-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (5.2 g); NMR Spectrum: ($DMSOd_6$) 1.9 (s, 9H), 1.4 (s, 9H), 1.95 (m, 2H), 2.32 (m, 4H), 2.45 (m, 2H), 3.3 (m, 4H), 3.9 (s, 3H), 4.2 (m, 2H), 5.9 (s, 2H), 7.18 (s, 1H), 7.5 (s, 1H), 8.35 (s, 1H); Mass Spectrum: $M+H^+$ 533.

A mixture of the material so obtained and a saturated methanolic ammonia solution (160 ml) was stirred at ambient temperature for 1.5 days. The mixture was evaporated and the residue was triturated under diethyl ether. The resultant solid was isolated, washed with diethyl ether and dried under vacuum. There was thus obtained 7-[3-(4-tert-butoxycarbonylpiperazin-1-yl)propoxy]-6-methoxy-3,4-dihydroquinazolin-4-one (3.6 g); NMR Spectrum: ($DMSOd_6$) 1.4 (s, 9H), 1.98 (m, 2H), 2.3 (m, 4H), 2.45 (m, 2H), 3.25-3.35 (m, 4H), 3.88 (s, 3H), 4.15 (m, 2H), 7.1 (s, 1H), 7.45 (s, 1H), 7.98 (s, 1H); Mass Spectrum: $M+H^+$ 419.

A mixture of the material so obtained, carbon tetrachloride (2.4 ml), triphenylphosphine (4.39 g) and 1,2-dichloroethane (160 ml) was stirred and heated to 70°C for 2 hours. The mixture was evaporated and the residue was purified by column chromatography on silica using a 5:4:1 mixture of methylene chloride, ethyl acetate and methanol as eluent. There was thus obtained 7-[3-(4-tert-butoxycarbonylpiperazin-

1-yl)propoxy]-4-chloro-6-methoxyquinazoline (3.33 g); NMR Spectrum: ($DMSOd_6$) 1.4 (s, 9H), 2.0 (m, 2H), 2.35 (m, 4H), 2.48 (m, 2H), 3.35 (m, 4H), 4.02 (s, 3H), 4.3 (m, 2H), 7.4 (s, 1H), 7.5 (s, 1H), 8.9 (s, 1H); Mass Spectrum: $M+H^+$ 437 and 439.

[5] The product gave the following characterising data: NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.35 (m, 2H), 3.15 (m, 2H), 3.35 (m, 2H), 3.55 (m, 2H), 3.8 (m, 2H), 3.9 (s, 3H), 4.0 (m, 2H), 4.05 (s, 3H), 4.35 (m, 2H), 7.45 (s, 1H), 7.46 (s, 1H), 7.8 (s, 1H), 8.25 (s, 1H), 8.9 (s, 1H); Mass Spectrum: $M+H^+$ 493 and 495.

The 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline used as a starting material was prepared as follows :-

A mixture of 2-amino-4-benzyloxy-5-methoxybenzamide (J. Med. Chem., 1977, 20, 146-149; 10 g), (3-dimethylamino-2-azaprop-2-en-1-ylidene)dimethylammonium chloride (Gold's reagent, 7.4 g) and dioxane (100 ml) was stirred and heated to reflux for 24 hours. Sodium acetate (3.02 g) and acetic acid (1.65 ml) were added and the reaction mixture was heated for a further 3 hours. The mixture was evaporated and water was added to the residue. The resultant solid was collected by filtration, washed with water and dried. The material was recrystallised from acetic acid to give 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (8.7 g).

A mixture of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (35 g), thionyl chloride (440 ml) and DMF (1.75 ml) was heated to reflux for 4 hours. The thionyl chloride was evaporated under vacuum and the residue was azeotroped with toluene three times. The residue was dissolved in N-methylpyrrolidin-2-one (250 ml) to give a solution of 7-benzyloxy-4-chloro-6-methoxyquinazoline.

Phenol (29.05 g) was dissolved in N-methylpyrrolidin-2-one (210 ml) and sodium hydride (60% dispersion in mineral oil; 11.025 g) was added in portions with cooling. The resultant mixture was stirred at ambient temperature for 3 hours. The resultant viscous suspension was diluted with N-methylpyrrolidin-2-one (180 ml) and stirred overnight. The above-mentioned solution of 7-benzyloxy-4-chloro-6-methoxyquinazoline was added and the resultant suspension was stirred and heated to 100°C for 2.5 hours. The mixture was allowed to cool to ambient temperature and poured into water (1.5 L) with vigorous stirring. The precipitate was collected by filtration, washed with water and dried under vacuum. The material so obtained was dissolved in methylene chloride and the solution was washed with brine and filtered through phase separating paper. The solution was evaporated under vacuum and the resultant residue was triturated under diethyl ether. There was thus obtained

7-benzyloxy-6-methoxy-4-phenoxyquinazoline (87.8 g); NMR Spectrum: ($CDCl_3$) 4.09 (s, 3H), 5.34 (s, 2H), 7.42 (m, 12H), 7.63 (s, 1H).

A mixture of a portion (36.95 g) of the material so obtained and trifluoroacetic acid (420 ml) was heated to reflux for 3 hours. The reaction mixture was allowed to cool and evaporated under vacuum. The residue was stirred mechanically under water, basified by the addition of a saturated aqueous sodium bicarbonate solution and stirred overnight. The water was decanted and the residual solid was suspended in acetone. After stirring, the white solid was collected by filtration, washed with acetone and dried to give 7-hydroxy-6-methoxy-4-phenoxyquinazoline (26.61 g); NMR Spectrum: ($DMSOd_6$) 3.97 (s, 3H), 7.22 (s, 1H), 7.3 (m, 3H), 7.47 (t, 2H), 7.56 (s, 1H), 8.47 (s, 1H), 10.7 (s, 1H).

A mixture of 7-hydroxy-6-methoxy-4-phenoxyquinazoline (25.27 g), 3-morpholinopropyl chloride (18.48 g), potassium carbonate (39.1 g) and DMF (750 ml) was stirred and heated to 90°C for 3 hours. The mixture was allowed to cool to ambient temperature and filtered. The filtrate was evaporated and the residue was triturated under ethyl acetate. There was thus obtained 6-methoxy-7-(3-morpholinopropoxy)-4-phenoxyquinazoline (31.4 g); NMR Spectrum: ($DMSOd_6$) 1.97 (m, 2H), 2.39 (t, 4H), 2.47 (t, 2H), 3.58 (t, 4H), 3.95 (s, 3H), 4.23 (t, 2H), 7.31 (m, 3H), 7.36 (s, 1H), 7.49 (t, 2H), 7.55 (s, 1H), 8.52 (s, 1H).

A mixture of the material so obtained and 6N aqueous hydrochloric acid solution (800 ml) was stirred and heated to reflux for 1.5 hours. The reaction mixture was decanted and concentrated to a volume of 250 ml. The mixture was basified to pH9 by the addition of a saturated aqueous sodium bicarbonate solution and extracted with methylene chloride (4x400 ml). The combined extracts were filtered through phase separating paper and the filtrate was evaporated. The resultant solid was triturated under ethyl acetate to give 6-methoxy-7-(3-morpholinopropoxy)-3,4-dihydroquinazolin-4-one (23.9 g); NMR Spectrum: ($DMSOd_6$) 1.91 (m, 2H), 2.34 (t, 4H), 2.42 (t, 2H), 3.56 (t, 4H), 3.85 (s, 3H), 4.12 (t, 2H), 7.11 (s, 1H), 7.42 (s, 1H), 7.96 (s, 1H), 12.01 (s, 1H).

A mixture of the material so obtained, thionyl chloride (210 ml) and DMF (1.8 ml) was heated to reflux for 1.5 hours. The thionyl chloride was removed by evaporation under vacuum and the residue was azeotroped with toluene three times. The residue was taken up in water and basified to pH8 by the addition of a saturated aqueous sodium bicarbonate solution. The resultant aqueous layer was extracted with methylene chloride (4x400 ml). The combined extracts were washed with water and with brine and dried over magnesium

sulphate. The solution was filtered and evaporated. The resultant solid was triturated under ethyl acetate to give 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (17.39 g); NMR Spectrum: ($CDCl_3$) 2.1-2.16 (m, 2H), 2.48 (br s, 4H), 2.57 (t, 2H), 3.73 (t, 4H), 4.05 (s, 3H), 4.29 (t, 2H), 7.36 (s, 1H), 7.39 (s, 1H), 8.86 (s, 1H).

The 3-morpholinopropyl chloride used as a reagent was obtained as follows :-

A mixture of morpholine (52.2 ml), 1-bromo-3-chloropropane (30 ml) and toluene (180 ml) was heated to 70°C for 3 hours. The solid was removed by filtration and the filtrate was evaporated under vacuum. The resultant oil was decanted from the additional solid which was deposited and the oil was purified by vacuum distillation to yield 3-morpholinopropyl chloride (37.91 g); NMR Spectrum: ($DMSOd_6$) 1.85 (m, 2H), 2.3 (t, 4H), 2.38 (t, 2H), 3.53 (t, 4H), 3.65 (t, 2H).

[6] The reaction mixture was cooled to ambient temperature and allowed to stand for 16 hours. Diethyl ether was added and the resultant precipitate was isolated, washed with diethyl ether and dried. The product gave the following characterising data: Mass Spectrum: $M+H^+$ 551 and 553.

The 7-(2-acetoxy-3-morpholinopropoxy)-4-chloro-6-methoxyquinazoline used as a starting material was prepared as follows :-

2,3-Epoxypropyl bromide (16.8 ml) was added to a stirred mixture of 7-hydroxy-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (International Patent Application WO 00/47212, within example 12 thereof; 40 g), potassium carbonate (36 g) and DMF (400 ml) and the resultant mixture was heated to 70°C for 1.5 hours. The mixture was poured into an ice/water mixture (1.5 L) and the precipitate was collected, washed with water (1.6 L) and with diethyl ether (500 ml) and dried under vacuum. There was thus obtained 7-(2,3-epoxypropoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (46.7 g) which was used without further purification.

A portion (8 g) of the material so obtained was dissolved in chloroform (120 ml) and morpholine (5.8 ml) was added. The reaction mixture was heated to reflux for 16 hours. The mixture was evaporated and the residue was purified by column chromatography on silica using a 19:1 mixture of methylene chloride and methanol as eluent. There was thus obtained 7-(2-hydroxy-3-morpholinopropoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (8.2 g); NMR Spectrum: ($CDCl_3$) 1.2 (s, 9H), 2.5 (m, 2H), 2.6 (m, 2H), 2.7 (m, 2H), 3.5 (br s, 1H), 3.75 (m, 4H), 3.95 (s, 3H), 4.15 (m, 2H), 4.25 (m, 1H), 5.95 (s, 2H), 7.15 (s, 1H), 7.65 (s, 1H), 8.2 (s, 1H).

A mixture of the material so obtained and a saturated methanolic ammonia solution (50 ml) was stirred at ambient temperature for 24 hours. The mixture was evaporated and the resultant solid was washed with diethyl ether. There was thus obtained 7-(2-hydroxy-3-morpholinopropoxy)-6-methoxy-3,4-dihydroquinazolin-4-one (6.34 g); NMR Spectrum: ($DMSOd_6$) 2.4 (m, 6H), 3.55 (m, 4H), 3.85 (s, 3H), 4.0 (m, 2H), 4.15 (m, 1H), 4.95 (br s, 1H), 7.15 (s, 1H), 7.45 (s, 1H), 7.95 (s, 1H).

A mixture of a portion (5.2 g) of the material so obtained, pyridine (1 ml) and acetic anhydride (20 ml) was stirred at ambient temperature for 30 minutes. The mixture was poured into a stirred ice/water mixture and the resultant mixture was stirred for 30 minutes. The mixture was cooled in an ice bath and a saturated aqueous sodium bicarbonate solution was slowly added to adjust the pH to 9. The mixture was extracted with methylene chloride and the organic extract was washed with water and with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 97:3 mixture of methylene chloride and methanol as eluent. There was thus obtained 7-(2-acetoxy-3-morpholinopropoxy)-6-methoxy-3,4-dihydroquinazolin-4-one (5 g); NMR Spectrum: ($DMSOd_6$) 2.05 (s, 3H), 2.4 (m, 4H), 2.6 (m, 2H), 3.55 (m, 4H), 3.85 (s, 3H), 4.35 (m, 2H), 5.25 (m, 1H), 7.2 (s, 1H), 7.45 (s, 1H), 8.0 (s, 1H); Mass Spectrum: $M+H^+$ 378.

A mixture of the material so obtained, thionyl chloride (60 ml) and DMF (0.5 ml) was heated to reflux for 1 hour. The mixture was evaporated, toluene was added and the mixture was again evaporated. The residue was partitioned between methylene chloride and a saturated aqueous sodium bicarbonate solution. The organic solution was washed with water and with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 97:3 mixture of methylene chloride and methanol as eluent. There was thus obtained 7-(2-acetoxy-3-morpholinopropoxy)-4-chloro-6-methoxyquinazoline (4.12 g); NMR Spectrum: ($CDCl_3$) 2.1 (s, 3H), 2.55 (m, 4H), 2.7 (d, 2H), 3.7 (m, 4H), 4.05 (s, 3H), 4.35 (m, 1H), 4.45 (m, 1H), 5.45 (m, 1H), 7.4 (d, 2H), 8.85 (s, 1H); Mass Spectrum: $M+H^+$ 396 and 398.

[7] The reaction mixture was cooled to ambient temperature and allowed to stand for 16 hours. Diethyl ether was added and the resultant precipitate was isolated, washed with diethyl ether and dried. The product gave the following characterising data: Mass Spectrum: $M+H^+$ 537 and 539.

The 7-[2-acetoxy-3-(N-isopropyl-N-methylamino)propoxy]-4-chloro-6-methoxyquinazoline used as a starting material was prepared from 7-(2,3-epoxypropoxy)-

6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one and N-isopropyl-N-methylamine using an analogous sequence of reactions as those described in Note [6] immediately above. The required starting material gave the following characterising data: NMR Spectrum: ($CDCl_3$) 1.0 (d, 6H), 2.1 (s, 3H), 2.3 (s, 3H), 2.6 (m, 1H), 2.75 (m, 1H), 2.85 (m, 1H), 4.05 (s, 3H), 4.35 (m, 1H), 4.45 (m, 1H), 5.35 (m, 1H), 7.25 (s, 1H), 7.4 (s, 1H), 8.85 (s, 1H).

[8] The reaction mixture was cooled to ambient temperature and allowed to stand for 16 hours. Diethyl ether was added and the resultant precipitate was isolated, washed with diethyl ether and dried. The product gave the following characterising data: Mass Spectrum: $M+H^+$ 549 and 551.

The 7-(2-acetoxy-3-piperidinopropoxy)-4-chloro-6-methoxyquinazoline used as a starting material was prepared from 7-(2,3-epoxypropoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one and piperidine using an analogous sequence of reactions as those described in Note [6] immediately above. The required starting material gave the following characterising data: NMR Spectrum: ($CDCl_3$ and CD_3CO_2D) 1.6 (m, 2H), 1.9 (m, 4H), 2.1 (s, 3H), 3.2 (br s, 4H), 3.5 (m, 2H), 4.05 (s, 3H), 4.35 (m, 2H), 5.7 (m, 1H), 7.4 (s, 1H), 7.5 (s, 1H), 8.9 (s, 1H).

[9] The reaction mixture was cooled to ambient temperature and allowed to stand for 16 hours. Diethyl ether was added and the resultant precipitate was isolated, washed with diethyl ether and dried. The product gave the following characterising data: Mass Spectrum: $M+H^+$ 535 and 537.

The 7-(2-acetoxy-3-pyrrolidin-1-ylpropoxy)-4-chloro-6-methoxyquinazoline used as a starting material was prepared from 7-(2,3-epoxypropoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one and pyrrolidine using an analogous sequence of reactions as those described in Note [6] immediately above. The required starting material gave the following characterising data: NMR Spectrum: ($CDCl_3$ and CD_3CO_2D) 2.05 (s, 4H), 2.15 (s, 3H), 3.45 (br s, 4H), 3.65 (m, 2H), 4.05 (s, 3H), 4.4 (d, 2H), 5.65 (m, 1H), 7.4 (s, 1H), 7.55 (s, 1H), 8.9 (s, 1H).

[10] The reaction mixture was cooled to ambient temperature and allowed to stand for 16 hours. Diethyl ether was added and the resultant precipitate was isolated, washed with diethyl ether and dried. The product gave the following characterising data: Mass Spectrum: $M+H^+$ 589 and 591.

The 7-[2-acetoxy-3-(4-cyanomethylpiperazin-1-yl)propoxy]-4-chloro-6-methoxyquinazoline used as a starting material was prepared from 7-(2,3-epoxypropoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one and 1-cyanomethylpiperazine using an analogous sequence of reactions as those described in Note [6] immediately above. The required starting material gave the following characterising data: NMR Spectrum: ($CDCl_3$) 2.1 (s, 3H), 2.65 (br s, 10H), 3.5 (s, 2H), 4.05 (s, 3H), 4.4 (m, 2H), 5.45 (m, 1H), 7.25 (s, 1H), 7.4 (s, 1H), 8.85 (s, 1H); Mass Spectrum: $M+H^+$ 434 and 436.

The 1-cyanomethylpiperazine used as a starting material was prepared as follows :-

A mixture of 1-(tert-butoxycarbonyl)piperazine (5 g), 2-chloroacetonitrile (1.9 ml), potassium carbonate (4 g) and DMF (20 ml) was stirred at ambient temperature for 16 hours. A saturated aqueous ammonium chloride solution was added and the mixture was extracted with ethyl acetate. The organic phase was dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using diethyl ether as eluent. There was thus obtained 1-(tert-butoxycarbonyl)-4-cyanomethylpiperazine as a solid (5.7 g); NMR Spectrum: ($CDCl_3$) 1.45 (s, 9H), 2.5 (m, 4H), 3.45 (m, 4H), 3.55 (s, 2H).

A mixture of the material so obtained, trifluoroacetic acid (20 ml) and methylene chloride (25 ml) was stirred at ambient temperature for 4 hours. The mixture was evaporated, toluene was added and the mixture was evaporated again. The residue was purified by column chromatography on silica using a 9:1 mixture of methylene chloride and methanol as eluent. There was thus obtained 1-cyanomethylpiperazine trifluoroacetate salt which was treated with solid sodium bicarbonate in a mixture of methylene chloride, ethyl acetate and methanol to give the free base form (2.9 g); NMR Spectrum: ($CDCl_3$ and $DMSOd_6$) 2.7 (m, 4H), 3.2 (m, 4H), 3.6 (s, 2H), 6.2 (br s, 1H).

Example 3 **4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-(2-hydroxy-3-piperidinopropoxy)quinazoline dihydrochloride salt**

A mixture of 7-(2-acetoxy-3-piperidinopropoxy)-4-(2,4-dichloro-5-methoxyanilino)-6-methoxyquinazoline dihydrochloride (0.062 g) and a saturated methanolic ammonia solution (3 ml) was stirred at ambient temperature for 16 hours. The mixture was evaporated and the residue was purified by column chromatography on silica (Isolute sorbent from International Sorbent Technology Ltd., ref 9470-0100) using a 19:1 mixture of methylene chloride and methanol as eluent. The material so obtained was dissolved in methylene chloride (3 ml) and a 6M solution of hydrogen chloride in isopropanol (0.3ml) was added. Diethyl ether (10 ml)

was added and the precipitate was collected, washed with diethyl ether and dried under vacuum. There was thus obtained the title compound (0.054 g); NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 1.35-1.52 (m, 1H), 1.55-1.77 (m, 2H), 1.78-1.93 (m, 3H), 2.93-3.12 (m, 2H), 3.20-3.38 (m, 2H), 3.47-3.63 (m, 2H), 3.89 (s, 3H), 4.03 (s, 3H), 4.25 (d, 2H), 4.45-4.56 (m, 1H), 7.45 (s, 1H), 7.48 (s, 1H), 8.20 (s, 1H), 8.88 (s, 1H).

Example 4 4-(2,4-dichloro-5-methoxyanilino)-7-[2-hydroxy-3-(N-isopropyl-N-methylamino)propoxy]-6-methoxyquinazoline dihydrochloride salt

Using an analogous procedure to that described in Example 3, 7-[2-acetoxy-3-(N-isopropyl-N-methylamino)propoxy]-4-(2,4-dichloro-5-methoxyanilino)-6-methoxyquinazoline dihydrochloride was reacted with a saturated methanolic ammonia solution to give the title compound; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 1.22-1.35 (m, 6H), 2.80 (s, 3H), 3.05-3.48 (m, 2H), 3.65-3.73 (m, 1H), 3.89 (s, 3H), 4.03 (s, 3H), 4.22-4.3 (m, 2H), 4.39-4.49 (m, 1H), 7.44 (s, 1H), 7.47 (s, 1H), 7.85 (s, 1H), 8.21 (s, 1H), 8.87 (s, 1H).

Src Inhibitors described within International Patent Application PCT/GB 02/02128

Example 1 4-(2-chloro-5-methoxyanilino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline dihydrochloride salt

A mixture of 4-chloro-7-[3-(4-methylpiperazin-1-yl)propoxy]-6-methoxyquinazoline (0.1 g), 2-chloro-5-methoxyaniline (0.072 g), a 0.1M solution of hydrogen chloride in isopropanol (4 ml) and isopropanol (5 ml) was stirred and heated to 80°C for 2 hours. The mixture was cooled to ambient temperature and diethyl ether was added. The resultant solid was isolated, washed with diethyl ether and dried under vacuum. There was thus obtained the title compound (0.108 g); NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.35 (m, 2H), 2.9 (s, 3H), 3.4-4.0 (m, 10H), 3.8 (s, 3H), 4.0 (s, 3H), 4.35 (m, 2H), 7.05 (m, 1H), 7.15 (d, 1H), 7.4 (s, 1H), 7.55 (d, 1H), 8.2 (s, 1H), 8.8 (s, 1H); Mass Spectrum: $M+H^+$ 472 and 474.

The 4-chloro-7-[3-(4-methylpiperazin-1-yl)propoxy]-6-methoxyquinazoline used as a starting material was prepared as follows :-

A mixture of 3-bromopropanol (20 ml), N-methylpiperazine (29 ml), potassium carbonate (83 g) and ethanol (200 ml)was stirred and heated to reflux for 20 hours. The mixture was cooled to ambient temperature and filtered. The filtrate was evaporated and the residue was triturated under diethyl ether. The resultant mixture was filtered and the filtrate

was evaporated. The residue was purified by distillation at about 60-70°C under about 0.2 mm Hg to give 1-(3-hydroxypropyl)-4-methylpiperazine (17 g); NMR Spectrum: ($CDCl_3$) 1.72 (m, 2H), 2.3 (s, 3H), 2.2-2.8 (m, 8H), 2.6 (t, 2H), 3.8 (t, 2H), 5.3 (br s, 1H).

4-Toluenesulphonyl chloride (3.2 g) was added to a stirred mixture of 1-(3-hydroxypropyl)-4-methylpiperazine (2.4 g), triethylamine (4.6 ml) and methylene chloride (60 ml) and the resultant mixture was stirred at ambient temperature for 2 hours. The solution was washed in turn with a saturated aqueous sodium bicarbonate solution and with water and filtered through phase separating paper. The organic filtrate was evaporated to give 3-(4-methylpiperazin-1-yl)propyl 4-toluenesulphonate as an oil which crystallised on standing (3.7 g); Mass Spectrum: $M+H^+$ 313.

A mixture of 2-amino-4-benzyloxy-5-methoxybenzamide (J. Med. Chem., 1977, 20, 146-149; 10 g), (3-dimethylamino-2-azaprop-2-en-1-ylidene)dimethylammonium chloride (Gold's reagent, 7.4 g) and dioxane (100 ml) was stirred and heated to reflux for 24 hours. Sodium acetate (3.02 g) and acetic acid (1.65 ml) were added and the reaction mixture was heated for a further 3 hours. The mixture was evaporated and water was added to the residue. The resultant solid was collected by filtration, washed with water and dried. The material was recrystallised from acetic acid to give 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (8.7 g).

After repetition of the reaction so described, a mixture of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (20.3 g), thionyl chloride (440 ml) and DMF (1.75 ml) was heated to reflux for 4 hours. The thionyl chloride was evaporated under vacuum and the residue was azeotroped with toluene three times to give 7-benzyloxy-4-chloro-6-methoxyquinazoline.

A mixture of the 7-benzyloxy-4-chloro-6-methoxyquinazoline so obtained, potassium carbonate (50 g) and 4-chloro-2-fluorophenol (8.8 ml) and DMF (500 ml) was stirred and heated to 100°C for 5 hours. The mixture was allowed to cool to ambient temperature, poured into water (2 L) and stirred at ambient temperature for a few minutes. The resultant solid was isolated and washed with water. The solid was dissolved in methylene chloride and the solution was filtered and treated with decolourising charcoal. The resultant solution was filtered and evaporated to give a solid which was triturated under diethyl ether. There was thus obtained 7-benzyloxy-4-(4-chloro-2-fluorophenoxy)-6-methoxyquinazoline (23.2 g); NMR Spectrum: ($DMSOd_6$) 3.98 (s, 3H), 5.34 (s, 2H), 7.42 (m, 9H), 7.69 (m, 1H), 8.55 (s, 1H).

A mixture of the material so obtained and trifluoroacetic acid (15 ml) was heated to reflux for 3 hours. The reaction mixture was allowed to cool, toluene was added and the mixture was evaporated. The residue was triturated under diethyl ether and then under acetone. The resultant precipitate was isolated and dried to give 4-(4-chloro-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline trifluoroacetate salt (21.8 g) which was used without further purification.

A mixture of the trifluoroacetic acid salt of 4-(4-chloro-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline (3.2 g), 3-(4-methylpiperazin-1-yl)propyl 4-toluenesulphonate (3.0 g), potassium carbonate (6.1 g) and DMF (60 ml) was stirred at 90°C for 5 hours. The resultant mixture was cooled to ambient temperature, poured into water (700 ml) and extracted with ethyl acetate (5 times). The combined extracts were washed in turn with water, a saturated aqueous sodium bicarbonate solution, water and brine. The ethyl acetate solution was dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 100: 8:1 mixture of methylene chloride, methanol and a concentrated aqueous ammonium hydroxide solution (0.880 g/ml) as eluent. The material so obtained was triturated under diethyl ether. There was thus obtained 4-(4-chloro-2-fluorophenoxy)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline (1.64 g); NMR Spectrum: ($DMSOd_6$) 1.95 (m, 2H), 2.14 (s, 3H), 2.35 (m, 8H), 2.44 (t, 2H), 3.96 (s, 3H), 4.22 (t, 2H), 7.38 (s, 1H), 7.4 (m, 1H), 7.54 (m, 2H), 7.68 (m, 1H), 8.55 (s, 1H).

After repetition of the previous reaction, a mixture of 4-(4-chloro-2-fluorophenoxy)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline (2.6 g) and 2N aqueous hydrochloric acid solution (45 ml) was stirred and heated to 95°C for 2 hours. The mixture was cooled to ambient temperature and basified by the addition of solid sodium bicarbonate The mixture was evaporated and the residue was purified by column chromatography on silica using a 50: 8:1 mixture of methylene chloride, methanol and a concentrated aqueous ammonium hydroxide solution (0.880 g/ml) as eluent. There was thus obtained 6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]-3,4-dihydroquinazolin-4-one (1.8 g); Mass Spectrum: $M+H^+$ 333.

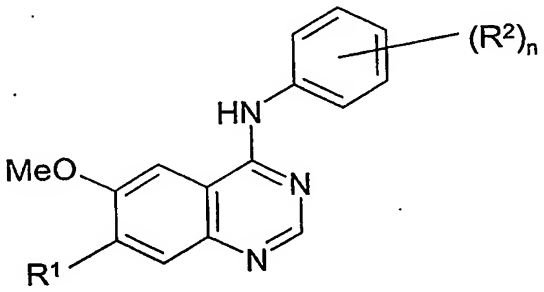
After repetition of the previous reaction, a mixture of 6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]-3,4-dihydroquinazolin-4-one (2.15 g), thionyl chloride (25 ml) and DMF (0.18 ml) was stirred and heated to reflux for 2 hours. The thionyl chloride was evaporated under vacuum and the residue azeotroped twice with toluene. The residue was taken up in water, basified by the addition of a saturated aqueous sodium bicarbonate

solution and extracted with methylene chloride (4 times). The combined extracts were washed in turn with water and brine and filtered through phase separating paper. The filtrate was evaporated under vacuum and the residue was purified by column chromatography on silica using a 100: 8:1 mixture of methylene chloride, methanol and a concentrated aqueous ammonium hydroxide solution (0.880 g/ml) as eluent. The solid so obtained was triturated under acetone, filtered and dried to give 4-chloro-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline (1.2 g); Mass Spectrum: $M+H^+$ 351.

Example 2

Using an analogous procedure to that described in Example 1, the appropriate 4-chloroquinazoline was reacted with the appropriate aniline to give the compounds described in Table I. Unless otherwise stated, each compound described in Table I was obtained as a dihydrochloride salt.

Table I



Compound No. & Note	R^1	$(R^2)_n$
[1]	2-piperidinoethoxy	2-chloro-5-methoxy
[2]	3-morpholinopropoxy	2-bromo-5-methoxy
[3]	3-morpholinopropoxy	2-chloro-5-methoxy
[4]	3-piperazin-1-ylpropoxy	2-chloro-5-methoxy
[5]	3-piperazin-1-ylpropoxy	2-bromo-5-methoxy

Notes

[1] The product gave the following characterising data: NMR Spectrum: ($DMSOd_6$) 1.4 (m, 1H), 1.65-1.9 (m, 5H), 3.1 (m, 2H), 3.6 (m, 4H), 3.8 (s, 3H), 4.05 (s, 3H), 4.7 (m, 2H),

7.05 (m, 1H), 7.15 (d, 1H), 7.5 (s, 1H), 7.55 (d, 1H), 8.3 (s, 1H), 8.85 (s, 1H); Mass Spectrum: $M+H^+$ 443 and 445.

The 4-chloro-6-methoxy-7-(2-piperidinoethoxy)quinazoline used as a starting material is described in International Patent Application WO 00/47212, example 180.

[2] The product gave the following characterising data: NMR Spectrum: (DMSOd_6 and CF_3CO_2D) 2.35 (m, 2H), 3.15 (m, 2H), 3.35 (m, 2H), 3.55 (m, 2H), 3.75 (m, 2H), 3.8 (s, 3H), 4.0 (m, 5H), 4.35 (m, 2H), 7.0 (m, 1H), 7.15 (d, 1H), 7.4 (s, 1H), 7.7 (d, 1H), 8.2 (s, 1H), 8.8 (s, 1H); Mass Spectrum: $M+H^+$ 503 and 505.

The 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline used as a starting material was prepared as follows :-

A mixture of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (35 g), thionyl chloride (440 ml) and DMF (1.75 ml) was heated to reflux for 4 hours. The thionyl chloride was evaporated under vacuum and the residue was azeotroped with toluene three times. The residue was dissolved in N-methylpyrrolidin-2-one (250 ml) to give a solution of 7-benzyloxy-4-chloro-6-methoxyquinazoline.

Phenol (29.05 g) was dissolved in N-methylpyrrolidin-2-one (210 ml) and sodium hydride (60% dispersion in mineral oil; 11.025 g) was added in portions with cooling. The resultant mixture was stirred at ambient temperature for 3 hours. The resultant viscous suspension was diluted with N-methylpyrrolidin-2-one (180 ml) and stirred overnight. The above-mentioned solution of 7-benzyloxy-4-chloro-6-methoxyquinazoline was added and the resultant suspension was stirred and heated to 100°C for 2.5 hours. The mixture was allowed to cool to ambient temperature and poured into water (1.5 L) with vigorous stirring. The precipitate was collected by filtration, washed with water and dried under vacuum. The material so obtained was dissolved in methylene chloride and the solution was washed with brine and filtered through phase separating paper. The solution was evaporated under vacuum and the resultant residue was triturated under diethyl ether. There was thus obtained 7-benzyloxy-6-methoxy-4-phenoxyquinazoline (87.8 g); NMR Spectrum: ($CDCl_3$) 4.09 (s, 3H), 5.34 (s, 2H), 7.42 (m, 12H), 7.63 (s, 1H).

A mixture of a portion (36.95 g) of the material so obtained and trifluoroacetic acid (420 ml) was heated to reflux for 3 hours. The reaction mixture was allowed to cool and evaporated under vacuum. The residue was stirred mechanically under water, basified by the addition of a saturated aqueous sodium bicarbonate solution and stirred overnight. The water was decanted and the residual solid was suspended in acetone. After stirring, the white solid

was collected by filtration, washed with acetone and dried to give 7-hydroxy-6-methoxy-4-phenoxyquinazoline (26.61 g); NMR Spectrum: ($DMSOd_6$) 3.97 (s, 3H), 7.22 (s, 1H), 7.3 (m, 3H), 7.47 (t, 2H), 7.56 (s, 1H), 8.47 (s, 1H), 10.7 (s, 1H).

A mixture of 7-hydroxy-6-methoxy-4-phenoxyquinazoline (25.27 g), 3-morpholinopropyl chloride (18.48 g), potassium carbonate (39.1 g) and DMF (750 ml) was stirred and heated to 90°C for 3 hours. The mixture was allowed to cool to ambient temperature and filtered. The filtrate was evaporated and the residue was triturated under ethyl acetate. There was thus obtained 6-methoxy-7-(3-morpholinopropoxy)-4-phenoxyquinazoline (31.4 g); NMR Spectrum: ($DMSOd_6$) 1.97 (m, 2H), 2.39 (t, 4H), 2.47 (t, 2H), 3.58 (t, 4H), 3.95 (s, 3H), 4.23 (t, 2H), 7.31 (m, 3H), 7.36 (s, 1H), 7.49 (t, 2H), 7.55 (s, 1H), 8.52 (s, 1H).

A mixture of the material so obtained and 6N aqueous hydrochloric acid solution (800 ml) was stirred and heated to reflux for 1.5 hours. The reaction mixture was decanted and concentrated to a volume of 250 ml. The mixture was basified to pH9 by the addition of a saturated aqueous sodium bicarbonate solution and extracted with methylene chloride (4x400 ml). The combined extracts were filtered through phase separating paper and the filtrate was evaporated. The resultant solid was triturated under ethyl acetate to give 6-methoxy-7-(3-morpholinopropoxy)-3,4-dihydroquinazolin-4-one (23.9 g); NMR Spectrum: ($DMSOd_6$) 1.91 (m, 2H), 2.34 (t, 4H), 2.42 (t, 2H), 3.56 (t, 4H), 3.85 (s, 3H), 4.12 (t, 2H), 7.11 (s, 1H), 7.42 (s, 1H), 7.96 (s, 1H), 12.01 (s, 1H).

A mixture of the material so obtained, thionyl chloride (210 ml) and DMF (1.8 ml) was heated to reflux for 1.5 hours. The thionyl chloride was removed by evaporation under vacuum and the residue was azeotroped with toluene three times. The residue was taken up in water and basified to pH8 by the addition of a saturated aqueous sodium bicarbonate solution. The resultant aqueous layer was extracted with methylene chloride (4x400 ml). The combined extracts were washed with water and with brine and dried over magnesium sulphate. The solution was filtered and evaporated. The resultant solid was triturated under ethyl acetate to give 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (17.39 g); NMR Spectrum: ($CDCl_3$) 2.1-2.16 (m, 2H), 2.48 (br s, 4H), 2.57 (t, 2H), 3.73 (t, 4H), 4.05 (s, 3H), 4.29 (t, 2H), 7.36 (s, 1H), 7.39 (s, 1H), 8.86 (s, 1H).

The 3-morpholinopropyl chloride used as a reagent was obtained as follows :-

A mixture of morpholine (52.2 ml), 1-bromo-3-chloropropane (30 ml) and toluene (180 ml) was heated to 70°C for 3 hours. The solid was removed by filtration and the filtrate

was evaporated under vacuum. The resultant oil was decanted from the additional solid which was deposited and the oil was purified by vacuum distillation to yield 3-morpholinopropyl chloride (37.91 g); NMR Spectrum: ($DMSOd_6$) 1.85 (m, 2H), 2.3 (t, 4H), 2.38 (t, 2H), 3.53 (t, 4H), 3.65 (t, 2H).

The 2-bromo-5-methoxyaniline used as a starting material was obtained as follows ;-

A mixture of hydrazine hydrate (1 ml), Raney nickel (0.13 g) and methanol was stirred and heated to reflux and a solution of 2-bromo-5-methoxy-1-nitrobenzene (1 g) in methanol (18 ml) was added dropwise. The resultant mixture was heated to reflux for a further 15 minutes. The reaction mixture was cooled to ambient temperature, filtered and evaporated. The residue was partitioned between methylene chloride and water. The organic phase was dried over magnesium sulphate and evaporated to give 2-bromo-5-methoxyaniline (0.8 g); NMR Spectrum: ($DMSOd_6$) 3.65 (s, 3H), 5.25 (br s, 2H), 6.1 (m, 1H), 6.4 (d, 1H), 7.2 (d, 1H).

[3] The product gave the following characterising data: NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.35 (m, 2H), 3.1 (m, 2H), 3.3 (m, 2H), 3.5 (m, 2H), 3.8 (s, 3H), 3.9 (m, 2H), 3.95 (m, 2H), 4.05 (s, 3H), 4.35 (m, 2H), 7.05 (m, 1H), 7.15 (d, 1H), 7.45 (s, 1H), 7.55 (d, 1H), 8.3 (s, 1H), 8.8 (s, 1H); Mass Spectrum: $M+H^+$ 459 and 461.

[4] 7-[3-(4-tert-Butoxycarbonylpiperazin-1-yl)propoxy]-4-chloro-6-methoxyquinazoline was used as the appropriate 4-chloroquinazoline. The product gave the following characterising data: NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.4 (m, 2H), 3.4-3.9 (br m, 10H), 3.8 (s, 3H), 4.05 (s, 3H), 4.4 (m, 2H), 7.1 (m, 1H), 7.2 (d, 1H), 7.4 (s, 1H), 7.6 (d, 1H), 8.2 (s, 1H), 8.9 (s, 1H); Mass Spectrum: $M-H^-$ 456 and 458.

The 7-[3-(4-tert-butoxycarbonylpiperazin-1-yl)propoxy]-4-chloro-6-methoxyquinazoline used as a starting material was obtained as follows :-

A mixture of 7-(3-bromopropoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (International Patent Application WO 00/47212, example 67; 4.5 g), tert-butyl piperazine-1-carboxylate (2.16 g), sodium iodide (0.079 g), potassium carbonate (2.9 g) and acetonitrile (150 ml) was stirred and heated to reflux for 8 hours. The resultant mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography on silica using a 19:1 mixture of methylene chloride and methanol as eluent. There was thus obtained 7-[3-(4-tert-butoxycarbonylpiperazin-1-yl)propoxy]-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (5.2 g); NMR Spectrum: ($DMSOd_6$) 1.9 (s, 9H), 1.4 (s, 9H), 1.95 (m, 2H), 2.32 (m, 4H), 2.45 (m, 2H), 3.3 (m, 4H), 3.9

(s, 3H), 4.2 (m, 2H), 5.9 (s, 2H), 7.18 (s, 1H), 7.5 (s, 1H), 8.35 (s, 1H); Mass Spectrum: $M+H^+$ 533.

A mixture of the material so obtained and a saturated methanolic ammonia solution (160 ml) was stirred at ambient temperature for 1.5 days. The mixture was evaporated and the residue was triturated under diethyl ether. The resultant solid was isolated, washed with diethyl ether and dried under vacuum. There was thus obtained 7-[3-(4-tert-butoxycarbonylpiperazin-1-yl)propoxy]-6-methoxy-3,4-dihydroquinazolin-4-one (3.6 g); NMR Spectrum: ($DMSOd_6$) 1.4 (s, 9H), 1.98 (m, 2H), 2.3 (m, 4H), 2.45 (m, 2H), 3.25-3.35 (m, 4H), 3.88 (s, 3H), 4.15 (m, 2H), 7.1 (s, 1H), 7.45 (s, 1H), 7.98 (s, 1H); Mass Spectrum: $M+H^+$ 419.

A mixture of the material so obtained, carbon tetrachloride (2.4 ml), triphenylphosphine (4.39 g) and 1,2-dichloroethane (160 ml) was stirred and heated to 70°C for 2 hours. The mixture was evaporated and the residue was purified by column chromatography on silica using a 5:4:1 mixture of methylene chloride, ethyl acetate and methanol as eluent. There was thus obtained 7-[3-(4-tert-butoxycarbonylpiperazin-1-yl)propoxy]-4-chloro-6-methoxyquinazoline (3.33 g); NMR Spectrum: ($DMSOd_6$) 1.4 (s, 9H), 2.0 (m, 2H), 2.35 (m, 4H), 2.48 (m, 2H), 3.35 (m, 4H), 4.02 (s, 3H), 4.3 (m, 2H), 7.4 (s, 1H), 7.5 (s, 1H), 8.9 (s, 1H); Mass Spectrum: $M+H^+$ 437 and 439.

[5] 7-[3-(4-tert-Butoxycarbonylpiperazin-1-yl)propoxy]-4-chloro-6-methoxyquinazoline was used as the appropriate 4-chloroquinazoline. The product gave the following characterising data: NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.35 (m, 2H), 3.3-3.9 (br m, 10H), 3.8 (s, 3H), 4.05 (s, 3H), 4.35 (m, 2H), 7.05 (m, 1H), 7.2 (d, 1H), 7.4 (s, 1H), 7.7 (d, 1H), 8.2 (s, 1H), 8.85 (s, 1H); Mass Spectrum: $M+H^+$ 502 and 504.

Example 3 4-(2-chloro-5-methoxyanilino)-6-methoxy-7-(2-morpholinoethoxy)quinazoline

Diethyl azodicarboxylate (0.284 ml) was added dropwise to a stirred mixture of 4-(2-chloro-5-methoxyanilino)-7-hydroxy-6-methoxyquinazoline (0.3 g), 1-(2-hydroxyethyl)morpholine (0.104 ml), triphenylphosphine (0.474 g) and methylene chloride (30 ml) and the reaction mixture was stirred at ambient temperature for 1 hour. The mixture was evaporated and the residue was purified by column chromatography on silica using a 19:1 mixture of methylene chloride and methanol as eluent. There was thus obtained the title compound (0.299 g); NMR Spectrum: ($CDCl_3$) 2.65 (m, 4H), 2.95 (t, 2H), 3.75 (m,

4H), 3.9 (s, 3H), 4.05 (s, 3H), 4.35 (t, 2H), 6.6 (m, 1H), 7.05 (s, 1H), 7.3 (s, 1H), 7.35 (d, 1H), 7.8 (s, 1H), 8.55 (s, 1H), 8.75 (s, 1H); Mass Spectrum: $M+H^+$ 445 and 447.

The 4-(2-chloro-5-methoxyanilino)-7-hydroxy-6-methoxyquinazoline used as a starting material was obtained as follows :-

A mixture of 7-benzyloxy-4-chloro-6-methoxyquinazoline (4.3 g), 2-chloro-5-methoxyaniline (2.7 g), a 6.2M solution of hydrogen chloride in isopropanol (0.225 ml) and isopropanol (200 ml) was stirred and heated to 80°C for 2.5 hours. The mixture was cooled to 0°C and the precipitate was isolated, washed with in turn with isopropanol and diethyl ether and dried under vacuum. There was thus obtained 7-benzyloxy-4-(2-chloro-5-methoxyanilino)-6-methoxyquinazoline (4.73 g); NMR Spectrum: ($DMSOd_6$) 3.8 (s, 3H), 4.03 (s, 3H), 5.36 (s, 2H), 7.06 (m, 1H), 7.18 (d, 1H), 7.4-7.6 (m, 7H), 8.2 (s, 1H), 8.77 (s, 1H), 11.5 (br s, 1H); Mass Spectrum: $M+H^+$ 422 and 424.

A mixture of the material so obtained and trifluoroacetic acid (40 ml) was stirred and heated to 80°C for 4 hours. The mixture was poured into water and solid sodium bicarbonate was added to basify the mixture to pH8. The resultant precipitate was isolated, washed with water and dried under vacuum at 50°C for 48 hours. The material so obtained was purified by column chromatography on silica using a 1:1 mixture of methylene chloride and ethyl acetate as eluent. There was thus obtained 4-(2-chloro-5-methoxyanilino)-7-hydroxy-6-methoxyquinazoline (2.9 g); NMR Spectrum: ($DMSOd_6$) 3.8 (s, 3H), 4.0 (s, 3H), 6.95 (m, 1H), 7.1 (s, 1H), 7.15 (s, 1H), 7.5 (d, 1H), 7.8 (s, 1H), 8.3 (s, 1H), 9.5 (br s, 1H), 10.4 (br s, 1H).

Example 4 **4-(2-bromo-5-methoxyanilino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline**

Sodium hydride (60% in mineral oil; 0.034 g) was added to a stirred solution of 2-bromo-5-methoxyaniline (0.712 g) in DMF (3 ml) and the mixture was stirred at ambient temperature for 20 minutes. 4-Chloro-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline (0.15 g) was added and the reaction mixture was stirred at ambient temperature for 48 hours. The mixture was evaporated and the residue was partitioned between ethyl acetate and water. The organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated. The material so obtained was purified by column chromatography on silica using a 19:1 mixture of methylene chloride and a saturated

methanolic ammonia solution as eluent. There was thus obtained the title compound (0.06 g); NMR Spectrum: (DMSOd_6 and CF_3CO_2D) 2.3 (m, 2H), 2.9 (s, 3H), 3.25-4.0 (m, 10H), 3.8 (s, 3H), 4.0 (s, 3H), 4.3 (m, 2H), 7.05 (m, 1H), 7.2 (d, 1H), 7.35 (s, 1H), 7.75 (d, 1H), 8.15 (s, 1H), 8.85 (s, 1H), Mass Spectrum: $M+H^+$ 516 and 518.

Src Inhibitors described within International Patent Application PCT/GB 02/03177

Example 1

4-(6-chloro-2,3-methylenedioxyanilino)-7-(3-chloropropoxy)-3-cyano-6-methoxyquinoline

Sodium hexamethyldisilazane (1M solution in THF; 3.34 ml) was added to a solution of 6-chloro-2,3-methylenedioxyaniline (0.573 g) in DMF (12 ml) that was cooled to 0°C and the mixture was stirred for 5 minutes. A solution of 4-chloro-7-(3-chloropropoxy)-3-cyano-6-methoxyquinoline (0.5 g) in DMF (3 ml) was added and the resultant mixture was stirred at ambient temperature for 1 hour. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica increasingly polar mixtures of methylene chloride and ethyl acetate as eluent. There was thus obtained the title compound as a solid (0.62 g); NMR Spectrum: (DMSOd_6 at 60°C) 2.32 (m, 2H), 3.9 (m, 2H), 4.0 (s, 3H), 4.35 (m, 2H), 6.1 (s, 2H), 7.0 (d, 1H), 7.1 (d, 1H), 7.4 (s, 1H), 7.9 (s, 1H), 8.42 (s, 1H), 9.32 (s, 1H); Mass Spectrum: $M+H^+$ 446 and 448.

The 4-chloro-7-(3-chloropropoxy)-3-cyano-6-methoxyquinoline used as a starting material was prepared as follows :-

A mixture of 4-chloro-3-cyano-7-hydroxy-6-methoxyquinoline (0.2 g, prepared as described in International Patent Application WO 00/68201, disclosed as compound (7) within Preparation 1 therein), potassium tert-butoxide (0.1 g) and DMF (8 ml) was stirred at ambient temperature for 15 minutes. 1-Bromo-3-choropropane (0.134 g) was added and the reaction mixture was stirred at ambient temperature for 16 hours. The resultant mixture was evaporated and the residue was partitioned between methylene chloride and an aqueous sodium bicarbonate solution. The organic layer was dried using magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of ethyl acetate and hexane. There was thus obtained the required starting

material (0.131 g); NMR Spectrum: ($DMSOd_6$) 2.3 (m, 2H), 3.8 (m, 2H), 4.0 (s, 3H), 4.35 (m, 2H), 7.42 (s, 1H), 7.68 (s, 1H), 8.95 (s, 1H); Mass Spectrum: $M+H^+$ 311.

The 6-chloro-2,3-methylenedioxyaniline used as a starting material was prepared as follows :-

Sulphuryl chloride (72.5 ml) was added dropwise during 1.7 hours to a stirred mixture of benzodioxole (100 g), aluminium trichloride (0.43 g) and diphenyl sulphide (0.55 ml). Once the reaction started with the evolution of sulphur dioxide, the reaction mixture was cooled in a water bath to a temperature of approximately 22°C. After completion of the addition, the reaction mixture was stirred at ambient temperature for 45 minutes. The reaction mixture was degassed under vacuum and filtered and the filtrate was distilled at atmospheric pressure using a Vigreux distillation column. There was thus obtained 5-chloro-1,3-benzodioxole; b.p. 185-187°C; NMR Spectrum: ($CDCl_3$) 6.0 (s, 2H); 6.7 (d, 1H); 6.75-6.9 (m, 2H).

A mixture of diisopropylamine (4.92 ml) and THF (100 ml) was cooled to -78°C and n-butyllithium (2.5 M in hexane, 14 ml) was added dropwise. The mixture was stirred at -78°C for 15 minutes. 5-Chloro-1,3-benzodioxole (3.73 ml) was added dropwise and the reaction mixture was stirred at -78°C for 30 minutes. Dry carbon dioxide gas was bubbled into the reaction mixture for 30 minutes. The resultant reaction mixture was allowed to warm to ambient temperature and was stirred for a further hour. Water was added and the organic solvent was evaporated. The residue was acidified to pH2 by the addition of 2N aqueous hydrochloric acid solution. The resultant solid was isolated and washed in turn with water and diethyl ether. There was thus obtained 5-chloro-1,3-benzodioxole-4-carboxylic acid (5.4 g); NMR Spectrum: ($DMSOd_6$) 6.15 (s, 2H), 7.0 (m, 2H), 13.7 (br s, 1H).

A portion (1 g) of the material so obtained was dissolved in 1,4-dioxane (15 ml) and anhydrous tert-butanol (4 ml), diphenylphosphoryl azide (1.12 ml) and triethylamine (0.73 ml) were added in turn. The resultant mixture was stirred and heated to 100°C for 4 hours. The mixture was evaporated and the residue was partitioned between ethyl acetate and a 5% aqueous citric acid solution. The organic phase was washed in turn with water, a saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 9:1 mixture of petroleum ether (b.p. 40-60°C) and ethyl acetate as eluent. There was thus obtained tert-butyl N-(5-chloro-1,3-benzodioxol-4-yl)carbamate (1.1 g); NMR Spectrum: ($DMSOd_6$) 1.45 (s, 9H), 6.1 (s, 2H), 6.85 (d, 1H), 6.95 (d, 1H), 8.75 (s, 1H).

A mixture of the material so obtained (1.1 g), trifluoroacetic acid (6 ml) and methylene chloride (20 ml) was stirred at ambient temperature for 3 hours. The solvent was evaporated and the residue was partitioned between ethyl acetate and a saturated aqueous sodium bicarbonate solution. The organic phase was washed with brine, dried over magnesium sulphate and evaporated. There was thus obtained 6-chloro-2,3-methylenedioxyaniline (0.642 g); NMR Spectrum: ($DMSOd_6$) 5.15 (s, 2H), 6.0 (s, 2H), 6.25 (d, 1H), 6.75 (d, 1H).

Example 2

4-(6-chloro-2,3-methylenedioxyanilino)-3-cyano-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline

A mixture of 4-(6-chloro-2,3-methylenedioxyanilino)-7-(3-chloropropoxy)-3-cyano-6-methoxyquinoline (0.1 g), N-methylpiperazine (0.075 ml) and DMF (2 ml) was stirred and heated to 60°C for 24 hours. The cooled mixture was evaporated and the resultant residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and a saturated methanolic ammonia solution as eluent. There was thus obtained the title compound (0.051 g); NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.35 (m, 2H), 2.95 (s, 3H), 3.45 (m, 2H), 3.2-4.0 (m, 8H), 4.02 (s, 3H), 4.32 (m, 2H), 6.15 (m, 2H), 7.08 (d, 1H), 7.15 (d, 1H), 7.48 (s, 1H), 8.15 (s, 1H), 9.15 (s, 1H); Mass Spectrum: $M+H^+$ 511.

Example 3

7-(3-chloropropoxy)-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline

Using an analogous procedure to that described in Example 1, 4-chloro-7-(3-chloropropoxy)-3-cyano-6-methoxyquinoline was reacted with 2,3-methylenedioxyaniline to give the title compound as a solid (0.62 g); NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.4 (m, 2H), 3.85 (m, 2H), 3.95 (s, 3H), 4.3 (m, 2H), 6.0 (s, 2H), 6.8-7.0 (m, 2H), 7.35 (s, 1H), 7.8 (s, 1H), 8.45 (s, 1H), 9.6 (br s, 1H); Mass Spectrum: $M+H^+$ 412.

The 2,3-methylenedioxyaniline used as a starting material was prepared as follows :-

A mixture of 2,3-dihydroxybenzoic acid (5 g), methanol (50 ml) and concentrated sulphuric acid (10 drops) was stirred and heated to 60°C for 24 hours. The mixture was evaporated and the residue was taken up in ethyl acetate. The organic solution was washed with a saturated solution of sodium bicarbonate, dried over magnesium sulphate and

evaporated to give methyl 2,3-dihydroxybenzoate (2.19 g); NMR Spectrum: ($CDCl_3$) 3.95 (s, 3H), 5.7 (s, 1H), 6.8 (t, 1H), 7.15 (d, H), 7.35 (d, H).

After repetition of the previous reaction, a mixture of methyl 2,3-dihydroxybenzoate (2.8 g), potassium fluoride (4.8 g) and DMF (45 ml) was stirred at ambient temperature for 30 minutes. Dibromomethane (1.28 ml) was added and the mixture was heated to 120°C for 3 hours. The mixture was cooled to ambient temperature, poured into water and extracted with diethyl ether. The organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography using a 9:1 mixture of petroleum ether (b.p. 40-60°C) and ethyl acetate as eluent. There was thus obtained methyl 2,3-methylenedioxybenzoate (2.3 g) as a solid; NMR Spectrum: ($CDCl_3$) 3.95 (s, 3H), 6.1 (s, 2H), 6.85 (t, 1H), 7.0 (d, 1H), 7.45 (d, 1H).

A mixture of the material so obtained, a 2N aqueous potassium hydroxide solution (15.5 ml) and methanol (40 ml) was stirred at ambient temperature for 2 hours. The solution was concentrated to about one quarter of the original volume and cooled in an ice bath. The mixture was acidified to pH3.5 by the addition of a 2N aqueous hydrochloric acid solution. The resultant precipitate was collected by filtration and washed in turn with water and diethyl ether. There was thus obtained 2,3-methylenedioxybenzoic acid (1.87 g); NMR Spectrum: ($DMSOd_6$) 6.1 (s, 1H), 6.9 (t, 1H), 7.15 (d, 1H), 7.3 (d, 1H), 13.0 (br s, 1H).

The material so obtained was suspended in anhydrous dioxane (30 ml) and anhydrous diphenylphosphoryl azide (2.45 ml), triethylamine (1.6 ml) and tert-butanol (9 ml) were added. The mixture was heated to reflux for 5 hours. The mixture was cooled to ambient temperature, concentrated by evaporation and diluted with ethyl acetate. The organic phase was washed in turn with a 5% aqueous citric acid solution, water, an aqueous sodium bicarbonate solution and brine and dried over magnesium sulphate. The solvent was evaporated and the residue was purified by column chromatography on silica using a 19:1 mixture of petroleum ether (b.p. 40-60°C) and ethyl acetate as eluent. There was thus obtained tert-butyl N-(2,3-methylenedioxyphenyl)carbamate (1.98 g) as a solid; NMR Spectrum: ($CDCl_3$) 1.55 (s, 9H), 5.95 (s, 2H), 6.4 (br s, 1H), 6.55 (d, 1H), 6.8 (t, 1H), 7.45 (d, 1H).

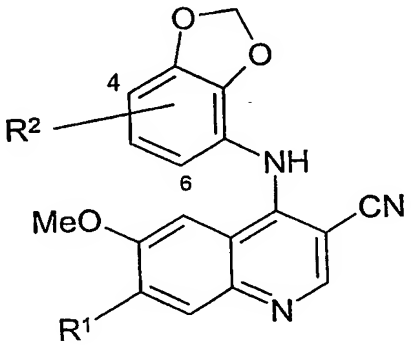
A 5N aqueous hydrochloric acid solution (30 ml) was added to a solution of tert-butyl N-(2,3-methylenedioxyphenyl)carbamate (1.9 g) in ethanol (38 ml) and the reaction mixture was stirred at ambient temperature for 20 hours. The ethanol was evaporated and the residual aqueous phase was washed with diethyl ether and neutralised to pH7 by the addition of solid

potassium hydroxide. The resultant mixture was filtered and the aqueous phase was extracted with diethyl ether. The organic phase was washed with brine, dried over magnesium sulphate and evaporated. There was thus obtained 2,3-methylenedioxyaniline (1.0 g) as an oil; NMR Spectrum: ($CDCl_3$) 3.0 (br s, 2H), 5.9 (s, 2H), 6.3 (m, 2H), 7.25 (t, 1H).

Example 4

Using an analogous procedure to that described in Example 2, the appropriate 7-(ω-haloalkoxy)-3-cyanoquinoline was reacted with the appropriate amine or heterocycle to give the compounds described in Table I. Unless otherwise stated, each compound described in Table I was obtained as a free base.

Table I



Compound No. & Note	R^1	R^2
[1]	3-(4-hydroxypiperidin-1-yl)propoxy	6-chloro
[2]	3-morpholinopropoxy	6-chloro
[3]	3-piperidinopropoxy	6-chloro
[4]	3-pyrrolidin-1-ylpropoxy	6-chloro
[5]	3-(4-acetylpiperazin-1-yl)propoxy	6-chloro
[6]	3-(4-methylsulphonylpiperazin-1-yl)propoxy	6-chloro
[7]	3-(4-cyanomethylpiperazin-1-yl)propoxy	6-chloro
[8]	3-(4-allylpiperazin-1-yl)propoxy	6-chloro
[9]	3-(4-methylpiperazin-1-yl)propoxy	hydrogen
[10]	3-(4-hydroxypiperidin-1-yl)propoxy	hydrogen
[11]	3-(4-acetylpiperazin-1-yl)propoxy	hydrogen

[12]	3-(4-methylsulphonylpiperazin-1-yl)propoxy	hydrogen
[13]	3-(4-cyanomethylpiperazin-1-yl)propoxy	hydrogen
[14]	3-(4-allylpiperazin-1-yl)propoxy	hydrogen
[15]	3-(N-methyl-N-prop-2-ynylamino)propoxy	hydrogen
[16]	2-(4-methylpiperazin-1-yl)ethoxy	hydrogen
[17]	2-(4-acetylpiperazin-1-yl)ethoxy	hydrogen
[18]	2-(4-allylpiperazin-1-yl)ethoxy	hydrogen
[19]	2-prop-2-ynylaminoethoxy	hydrogen
[20]	2-(N-methyl-N-prop-2-ynylamino)ethoxy	hydrogen
[21]	3-(3-fluoropyrrolidin-1-yl)propoxy	hydrogen
[22]	3-(3,3-difluoropyrrolidin-1-yl)propoxy	hydrogen
[23]	3-(4-fluoropiperidin-1-yl)propoxy	hydrogen
[24]	3-(4,4-difluoropiperidin-1-yl)propoxy	hydrogen
[25]	3-morpholinopropoxy	4-bromo
[26]	3-(4-tert-butoxycarbonylpiperazin-1-yl)propoxy	hydrogen
[27]	4-(4-methylpiperazin-1-yl)butoxy	hydrogen
[28]	4-(4-acetylpiperazin-1-yl)butoxy	6-chloro
[29]	3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy	hydrogen
[30]	4-(1,2,3,6-tetrahydropyridin-1-yl)butoxy	hydrogen
[31]	3-(2,5-dimethylpyrrol-1-yl)propoxy	hydrogen
[32]	3-(2,5-dimethyl-3-pyrrolin-1-yl)propoxy	hydrogen
[33]	(2S)-2-fluoro-3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy	hydrogen
[34]	(2S)-2-fluoro-3-morpholinopropoxy	hydrogen
[35]	3-morpholinopropoxy	4-(2-methoxyethyl)

Notes

[1] 4-Hydroxypiperidine was used as the heterocycle reactant. The reaction product was purified by column chromatography on reversed-phase silica using decreasingly polar mixtures of acetonitrile and a 1% solution of acetic acid in water. The material so obtained was dissolved in methylene chloride and the solution was dried over magnesium sulphate. The solution was filtered, the filtrate was evaporated and the residue was triturated under a

mixture of pentane and diethyl ether. The resultant precipitate was isolated and dried under vacuum. The product contained one equivalent of acetic acid and gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 1.5-1.7 (m, 1H), 1.8-1.95 (m, 2H), 1.95-2.1 (m, 1H), 2.2-2.35 (m, 2H), 3.05 (m, 1H), 3.15-3.45 (m, 4H), 3.55 (d, 1H), 3.7 (m, 1H), 4.0 (s, 3H), 4.3 (m, 2H), 6.15 (d, 2H), 7.08 (d, 1H), 7.15 (d, 1H), 7.45 (s, 1H), 8.15 (s, 1H), 9.15 (s, 1H); Mass Spectrum: $M+H^+$ 511.

[2] Morpholine was used as the heterocycle reactant. The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.35 (m, 2H), 3.2 (m, 2H), 3.4 (m, 2H), 3.6 (d, 2H), 3.75 (m, 2H), 4.05 (s, 3H), 4.08 (d, 2H), 4.35 (m, 2H), 6.2 (d, 2H), 7.15 (d, 1H), 7.2 (d, 1H), 7.5 (s, 1H), 8.2 (s, 1H), 9.2 (s, 1H); Mass Spectrum: $M+H^+$ 497 and 499.

[3] Piperidine was used as the heterocycle reactant. The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 1.45 (m, 1 H), 1.65-1.8 (m, 3H), 1.9 (d, 2H), 2.35 (m, 2H), 3.0 (m, 2H), 3.31 (m, 2H), 3.6 (d, 2H), 4.05 (s, 3H), 4.38 (m, 2H), 6.2 (d, 2H), 7.12 (d, 1H), 7.2 (d, 1H), 7.5 (s, 1H), 8.2 (s, 1H), 9.2 (s, 1H); Mass Spectrum: $M+H^+$ 495 and 497.

[4] Pyrrolidine was used as the heterocycle reactant. The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 1.9-2.0 (m, 2H), 2.1 (m, 2H), 2.35 (m, 2H), 3.05-3.2 (m, 2H), 3.45 (m, 2H), 3.75 (m, 2H), 4.08 (s, 3H), 4.35 (m, 2H), 6.2 (d, 2H), 7.12 (d, 1H), 7.2 (d, 1H), 7.5 (s, 1H), 8.2 (s, 1H), 9.2 (s, 1H); Mass Spectrum: $M+H^+$ 481 and 483.

[5] 1-Acetylpiperazine was used as the heterocycle reactant. The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.1 (s, 3H), 2.38 (m, 2H), 2.95-3.1 (m, 2H), 3.2 (m, 1H), 3.35-3.55 (m, 3H), 3.65 (d, 2H), 4.08 (s, 3H), 4.05-4.15 (m, 1H), 4.35 (m, 2H), 4.58 (d, 1H), 6.2 (d, 2H), 7.12 (d, 1H), 7.2 (d, 1H), 7.5 (s, 1H), 8.2 (s, 1H), 9.2 (s, 1H); Mass Spectrum: $M+H^+$ 538.

[6] 1-Methylsulphonylpiperazine was used as the heterocycle reactant. The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.3-2.4 (m, 2H), 3.08 (s, 3H), 3.12-3.35 (m, 4H), 3.45 (m, 2H), 3.75 (d, 2H), 3.85 (d, 2H), 4.05 (s, 3H), 4.35 (m, 2H), 6.2 (d, 2H), 7.15 (d, 1H), 7.2 (d, 1H), 7.5 (s, 1H), 8.2 (s, 1H), 9.2 (s, 1H); Mass Spectrum: $M+H^+$ 574 and 576.

The 1-methylsulphonylpiperazine used as a starting material was prepared as follows :-

Mesyl chloride (0.966 ml) was added dropwise to a stirred mixture of 1-benzylpiperazine (2 g), triethylamine (1.74 ml) and methylene chloride (30 ml) which was

cooled to 0°C. The reaction mixture was allowed to warm to ambient temperature and stirred for 1 hour. The mixture was partitioned between methylene chloride and water. The organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 7:3 mixture of methylene chloride and ethyl acetate as eluent. There was thus obtained 1-benzyl-4-methylsulphonylpiperazine (2.5 g) as a solid; NMR Spectrum: ($CDCl_3$) 2.6 (m, 4H), 2.8 (s, 3H), 3.3 (m, 4H), 3.55 (s, 2H), 7.3 (m, 5H); Mass Spectrum: $M+H^+$ 255.

A mixture of the material so obtained, cyclohexene (30 ml), palladium oxide on charcoal catalyst (20%; 0.5 g) and ethanol (70 ml) was stirred and heated to 80°C for 4 hours. The catalyst was removed by filtration and the solvent was evaporated to give 1-methylsulphonylpiperazine (1.58 g) as a solid; NMR Spectrum: ($CDCl_3$) 2.8 (s, 3H), 3.0 (m, 4H), 3.2 (m, 4H); Mass Spectrum: $M+H^+$ 165.

[7] 1-Cyanomethylpiperazine was used as the heterocycle reactant. The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.3-2.4 (m, 2H), 2.65-2.8 (m, 2H), 3.05-3.15 (m, 2H), 3.15-3.3 (m, 2H), 3.4 (m, 2H), 3.7 (br s, 2H), 3.9 (s, 2H), 4.1 (s, 3H), 4.35 (m, 2H), 6.2 (d, 2H), 7.12 (d, 1H), 7.2 (d, 1H), 7.5 (s, 1H), 8.2 (s, 1H), 9.2 (s, 1H); Mass Spectrum: $M+H^+$ 535 and 537.

The 1-cyanomethylpiperazine used as a starting material was prepared as follows :-

A mixture of 1-(tert-butoxycarbonyl)piperazine (5 g), 2-chloroacetonitrile (1.9 ml), potassium carbonate (4 g) and DMF (20 ml) was stirred at ambient temperature for 16 hours. A saturated aqueous ammonium chloride solution was added and the mixture was extracted with ethyl acetate. The organic phase was dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using diethyl ether as eluent. There was thus obtained 1-(tert-butoxycarbonyl)-4-cyanomethylpiperazine as a solid (5.7 g); NMR Spectrum: ($CDCl_3$) 1.45 (s, 9H), 2.5 (m, 4H), 3.45 (m, 4H), 3.55 (s, 2H).

A mixture of the material so obtained, trifluoroacetic acid (20 ml) and methylene chloride (25 ml) was stirred at ambient temperature for 4 hours. The mixture was evaporated, toluene was added and the mixture was evaporated again. The residue was purified by column chromatography on silica using a 9:1 mixture of methylene chloride and methanol as eluent. There was thus obtained 1-cyanomethylpiperazine trifluoroacetate salt which was treated with solid sodium bicarbonate in a mixture of methylene chloride, ethyl acetate and methanol to give the free base form (2.9 g); NMR Spectrum: ($CDCl_3$ and $DMSOd_6$) 2.7 (m, 4H), 3.2 (m, 4H), 3.6 (s, 2H), 6.2 (br s, 1H).

[8] 1-Allylpiperazine was used as the heterocycle reactant. The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.3-2.4 (m, 2H), 3.5 (m, 2H), 3.45-3.9 (m, 8H), 3.95 (d, 2H), 4.08 (s, 3H), 4.38 (m, 2H), 5.6-5.7 (m, 2H), 5.9-6.0 (m, 1H), 6.2 (d, 2H), 7.1 (d, 1H), 7.2 (d, 1H), 7.5 (s, 1H), 8.2 (s, 1H), 9.2 (s, 1H); Mass Spectrum: $M+H^+$ 536 and 538.

[9] 1-Methylpiperazine was used as the heterocycle reactant. The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.25-2.4 (m, 2H), 2.97 (s, 3H), 3.2-4.0 (m, 8H), 3.45 (m, 2H), 4.0 (s, 3H), 4.32 (m, 2H), 6.1 (s, 2H), 6.95-7.05 (m, 3H), 7.45 (s, 1H), 8.1 (s, 1H), 9.15 (s, 1H); Mass Spectrum: $M+H^+$ 476.

[10] The reaction product was purified by column chromatography on reversed-phase silica using decreasingly polar mixtures of acetonitrile and a 1% solution of acetic acid in water. The product contained one equivalent of acetic acid and gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 1.5-1.7 (m, 1H), 1.7-1.95 (m, 2H), 1.95-2.05 (m, 1H), 2.2-2.4 (m, 2H), 3.02 (m, 2H), 3.15-3.45 (m, 4H), 3.55 (d, 1H), 3.6 (m, 1H), 4.0 (s, 3H), 4.3 (m, 2H), 6.1 (s, 2H), 6.95-7.05 (m, 3H), 7.4 (s, 1H), 8.1 (s, 1H), 9.12 (s, 1H); Mass Spectrum: $M+H^+$ 477.

[11] The reaction product was purified by column chromatography on reversed-phase silica using decreasingly polar mixtures of acetonitrile and a 1% solution of acetic acid in water. The product contained 0.5 equivalents of acetic acid and gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.1 (s, 3H), 2.35 (m, 2H), 2.9-3.1 (m, 2H), 3.2 (m, 1H), 3.3-3.5 (m, 3H), 3.65 (d, 2H), 4.05 (s, 3H), 4.07 (m, 1H), 4.35 (m, 2H), 4.55 (d, 1H), 6.12 (s, 2H), 7.0-7.1 (m, 3H), 7.5 (s, 1H), 8.15 (s, 1H), 9.2 (s, 1H); Mass Spectrum: $M+H^+$ 504.

[12] The reaction product was purified by column chromatography on reversed-phase silica using decreasingly polar mixtures of acetonitrile and a 1% solution of acetic acid in water. The product contained 0.9 equivalents of acetic acid and gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.3-2.4 (m, 2H), 3.0 (s, 3H), 3.1-3.3 (m, 4H), 3.4 (m, 2H), 3.7 (d, 2H), 3.8 (d, 2H), 4.0 (s, 3H), 4.3 (m, 2H), 6.1 (s, 2H), 6.95-7.05 (m, 3H), 7.45 (s, 1H), 8.1 (s, 1H), 9.12 (s, 1H); Mass Spectrum: $M+H^+$ 540.

[13] The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.25-2.4 (m, 2H), 2.6-2.75 (m, 2H), 3.05 (d, 2H), 3.2 (m, 2H), 3.38 (m, 2H), 3.7 (d, 2H), 3.9 (s, 2H), 4.05 (s, 3H), 4.35 (m, 2H), 6.12 (s, 2H), 7.0-7.1 (m, 3H), 7.5 (s, 1H), 8.15 (s, 1H), 9.18 (s, 1H); Mass Spectrum: $M+H^+$ 501.

[14] The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.25-2.4 (m, 2H), 3.2-3.9 (m, 8H), 3.45 (m, 2H), 3.95 (d, 2H), 4.02 (s, 3H), 4.35 (m, 2H), 5.55-5.65 (m, 2H), 5.85-6.0 (m, 1H), 6.1 (s, 2H), 6.95-7.1 (m, 3H), 7.45 (s, 1H), 8.1 (s, 1H), 9.15 (s, 1H); Mass Spectrum: $M+H^+$ 502.

[15] The reactants were 7-(3-bromopropoxy)-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline (obtained as described in Example 8) and N-methyl-N-prop-2-ynylamine and the reaction mixture was stirred at ambient temperature for 24 hours. The material so obtained was dissolved in diethyl ether and a solution of hydrogen chloride in diethyl ether (1M, 2 ml) was added. The resultant solid was washed with diethyl ether. Thereby, the product was obtained as a dihydrochloride salt and gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 2.3 (m, 2H), 2.82 (s, 3H), 3.23-3.39 (m, 2H), 3.84 (m, 1H), 4.0 (s, 3H), 4.15 (d, 2H), 4.3 (t, 2H), 6.03 (s, 2H), 6.92-7.0 (m, 3H), 7.54 (s, 1H), 8.21 (s, 1H), 8.93 (s, 1H); Mass Spectrum: $M+H^+$ 445.

[16] 7-(2-Bromoethoxy)-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline (obtained as described in Example 9) was used as a reactant and the reaction mixture was stirred at ambient temperature for 24 hours rather than being heated to 60°C. The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.12 (s, 3H), 2.24–2.36 (m, 4H), 2.45–2.55 (m, 4H), 2.75 (t, 2H), 3.9 (s, 3H), 4.23 (t, 2H), 5.97 (s, 2H), 6.8-6.93 (m, 3H), 7.32 (s, 1H), 7.75 (s, 1H), 8.41 (s, 1H), 9.48 (s, 1H); Mass Spectrum: $M+H^+$ 462.

[17] 7-(2-Bromoethoxy)-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline was used as a reactant and the reaction mixture was stirred at ambient temperature for 24 hours. The material so obtained was dissolved in diethyl ether and a solution of hydrogen chloride in diethyl ether (1M, 2 ml) was added. The resultant solid was washed with diethyl ether. Thereby, the product was obtained as a dihydrochloride salt and gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.04 (s, 3H), 3.0-3.64 (m, 8H), 3.69 (m, 2H), 4.0 (s, 3H), 4.68 (m, 2H), 6.06 (s, 2H), 6.94-7.01 (m, 3H), 7.53 (s, 1H), 8.19 (s, 1H), 8.99 (s, 1H); Mass Spectrum: $M+H^+$ 477.

[18] 7-(2-Bromoethoxy)-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline was used as a reactant and the reaction mixture was stirred at ambient temperature for 24 hours. The material so obtained was dissolved in diethyl ether and a solution of hydrogen chloride in diethyl ether (1M, 2 ml) was added. The resultant solid was washed with diethyl ether. Thereby, the product was obtained as a dihydrochloride salt and gave the following

characterising data; NMR Spectrum: ($DMSOd_6$) 3.3-3.82 (m, 12H), 4.02 (s, 3H), 4.61 (m, 2H), 5.48-5.6 (m, 2H), 5.9-6.03 (m, 1H), 6.04 (s, 2H), 6.93-7.0 (m, 3H), 7.58 (s, 1H), 8.28 (s, 1H), 8.98 (s, 1H); Mass Spectrum: $M+H^+$ 488.

[19] 7-(2-Bromoethoxy)-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline was used as a reactant and the reaction mixture was stirred at ambient temperature for 24 hours. The material so obtained was dissolved in diethyl ether and a solution of hydrogen chloride in diethyl ether (1M, 2 ml) was added. The resultant solid was washed with diethyl ether. Thereby, the product was obtained as a dihydrochloride salt and gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 3.5 (m, 2H), 3.71 (m, 1H), 4.0 (s, 5H), 4.54 (m, 2H), 6.03 (s, 2H), 6.9-7.0 (m, 3H), 7.58 (s, 1H), 8.28 (s, 1H), 8.94 (s, 1H), 9.83 (br s, 1H); Mass Spectrum: $M+H^+$ 417.

[20] 7-(2-Bromoethoxy)-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline was used as a reactant and the reaction mixture was stirred at ambient temperature for 24 hours. The material so obtained was dissolved in diethyl ether and a solution of hydrogen chloride in diethyl ether (1M, 2 ml) was added. The resultant solid was washed with diethyl ether. Thereby, the product was obtained as a dihydrochloride salt and gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 2.92 (s, 3H), 3.69 (m, 2H), 3.85 (m, 1H), 4.02 (s, 3H), 4.22 (d, 2H), 4.67 (t, 2H), 6.04 (s, 2H), 6.92-7.0 (m, 3H), 7.6 (s, 1H), 8.34 (s, 1H), 8.95 (s, 1H); Mass Spectrum: $M+H^+$ 431.

[21] The reactants were 7-(3-bromopropoxy)-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline (0.25 g), 3-fluoropyrrolidine hydrochloride (Synthetic Letters, 1995, 1, 55-57; 0.134 g) and N,N-diisopropyl-N-ethylamine (0.4 ml) in 2-methoxyethanol (5 ml) and the mixture was stirred and heated to 85°C for 24 hours. The product (0.1 g) gave the following characterising data; NMR Spectrum: ($CDCl_3$) 1.26 (t, 2H), 1.95-2.25 (m, 4H), 2.44-2.51 (m, 1H), 2.68-2.74 (m, 3H), 2.79-2.95 (m, 3H), 3.7 (s, 3H), 4.25 (t, 2H), 5.06-5.28 (m, 1H), 5.94 (s, 2H), 6.62-6.65 (m, 2H), 6.73(d, 1H), 6.83 (t, 1H), 6.97 (s, 1H), 7.37 (s, 1H), 8.61 (s, 1H); Mass Spectrum: $M+H^+$ 465.

[22] The reactants were 7-(3-bromopropoxy)-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline (0.25 g), 3,3-difluoropyrrolidine hydrochloride (Synthetic Letters, 1995, 1, 55-57; 0.1 g) and N,N-diisopropyl-N-ethylamine (0.4 ml) in 2-methoxyethanol (5 ml) and the mixture was stirred and heated to 85°C for 24 hours. The reaction product was dissolved in diethyl ether and a solution of hydrogen chloride in diethyl ether (4M) was added. The resultant solid was washed with diethyl ether. Thereby, the

product was obtained as a dihydrochloride salt (0.16 g) and gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 2.21-2.38 (m, 2H), 2.54-2.74 (m, 2H), 3.43 (t, 2H), 3.62-4.26 (m, 5H), 4.32 (t, 2H), 6.06 (s, 2H), 6.94-7.03 (m, 3H), 7.57 (s, 1H), 8.26 (s, 1H), 8.98 (s, 1H), 11.22 (br s, 1H), 11.83-12.58 (m, 1H); Mass Spectrum: $M+H^+$ 483.

[23] The reactants were 7-(3-bromopropoxy)-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline (0.25 g), 4-fluoropiperidine hydrochloride (J. Org. Chem., 1979, 44, 771-777; 0.17 g) and N,N-diisopropyl-N-ethylamine (0.4 ml) in 2-methoxyethanol (5 ml) and the mixture was stirred and heated to 85°C for 24 hours. The product (0.13 g) gave the following characterising data; NMR Spectrum: ($CDCl_3$) 1.8-2.0 (m, 4H), 2.07-2.14 (m, 2H), 2.37-2.44 (m, 2H), 2.52-2.63 (m, 4H), 3.7 (s, 3H), 4.24 (t, 2H), 4.56-4.79 (m, 1H), 5.94 (s, 2H), 6.63 (d, 1H), 6.68 (s, 1H), 6.73 (d, 1H), 6.83 (t, 1H), 6.98 (s, 1H), 7.38 (s, 1H), 8.61 (s, 1H); Mass Spectrum: $M+H^+$ 479.

[24] The reactants were 7-(3-bromopropoxy)-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline (0.25 g), 4,4-difluoropiperidine (Tetrahedron, 1977, 33, 1707-1710; 0.154 g) and N,N-diisopropyl-N-ethylamine (0.4 ml) in 2-methoxyethanol (5 ml) and the mixture was stirred and heated to 85°C for 24 hours. The product (0.16 g) gave the following characterising data; NMR Spectrum: ($CDCl_3$) 1.93-2.17 (m, 6H), 2.54-2.62 (m, 6H), 3.7 (s, 3H), 4.24 (t, 2H), 5.94 (s, 2H), 6.6 (d, 1H), 6.69 (s, 1H), 6.73 (d, 1H), 6.83 (t, 1H), 6.98 (s, 1H), 7.38 (s, 1H), 8.61 (s, 1H); Mass Spectrum: $M+H^+$ 497.

[25] The reactants were 4-(4-bromo-2,3-methylenedioxyanilino)-7-(3-chloropropoxy)-3-cyano-6-methoxyquinoline and morpholine and the reaction mixture was heated to 50°C for 12 hours. The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 1.96 (m, 2H), 2.4-2.55 (m, 6H), 3.56 (s, 4H), 3.93 (s, 3H), 4.18 (t, 2H), 6.09 (s, 2H), 6.84 (d, 1H), 7.09 (d, 1H), 7.3 (s, 1H), 7.74 (s, 1H), 8.43 (s, 1H), 9.55 (s, 1H); Mass Spectrum: $M+H^+$ 541 and 543.

The 4-(4-bromo-2,3-methylenedioxyanilino)-7-(3-chloropropoxy)-3-cyano-6-methoxyquinoline used as a starting material was prepared as follows :-

N-Bromosuccimide (0.23 g) was added to a solution of 2,3-methylenedioxyaniline (0.17 g) in acetonitrile (10 ml) and the mixture was stirred at ambient temperature for 12 hours. The mixture was evaporated and the residue was purified by column chromatography on silica using increasingly polar mixtures of hexane and methylene chloride as eluent. There was thus obtained 4-bromo-2,3-methylenedioxyaniline as a solid (0.14 g); NMR Spectrum: ($DMSOd_6$) 5.04 (s, 2H), 5.98 (s, 2H), 6.02 (d, 1H), 6.7 (d, 1H).

A mixture of 4-bromo-2,3-methylenedioxyaniline (0.91 g), 4-chloro-7-(3-chloropropoxy)-3-cyano-6-methoxyquinoline (1.2 g) and 1-propanol (20 ml) was stirred and heated to reflux for 7 hours. The resultant solid was isolated and washed with diethyl ether. There was thus obtained 4-(4-bromo-2,3-methylenedioxyanilino)-7-(3-chloropropoxy)-3-cyano-6-methoxyquinoline as a solid (1.45 g); NMR Spectrum: ($DMSOd_6$) 2.28 (m, 2H), 3.83 (t, 2H), 3.99 (s, 3H), 4.31 (t, 2H), 6.13 (s, 2H), 6.92 (d, 1H), 7.18 (d, 1H), 7.43 (s, 1H), 8.04 (s, 1H), 8.95 (s, 1H); Mass Spectrum: $M+H^+$ 490.

[26] The reactants were 7-(3-chloropropoxy)-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline and 1-(tert-butoxycarbonyl)piperazine. Moreover, 2-methoxyethanol was used in place of DMF and the reaction mixture was heated to 110°C for 12 hours. The product gave the following characterising data; NMR Spectrum: ($CDCl_3$) 1.48 (s, 9H), 2.1 (m, 2H), 2.41 (m, 4H), 2.53 (t, 2H), 2.83 (m, 4H), 3.73 (s, 3H), 4.28 (t, 2H), 5.94 (s, 2H), 6.61-6.88 (m, 4H), 6.98 (s, 1H), 7.38 (s, 1H), 8.64 (s, 1H); Mass Spectrum: $M+H^+$ 562.

[27] The reactants were 7-(4-chlorobutoxy)-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline hydrochloride salt and 1-methylpiperazine. Moreover, 1-propanol was used in place of DMF and the reaction mixture was heated to 90°C for 18 hours. The reaction product was dissolved in ethyl acetate and a solution of hydrogen chloride in diethyl ether (4M, 1 ml) was added. The resultant solid was isolated and washed with diethyl ether. Thereby, the product was obtained as a dihydrochloride salt and gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 1.9-1.95 (m, 4H), 2.81 (br s, 3H), 3.2-3.8 (m, 10H), 4.02 (s, 3H), 4.22 (br s, 2H), 6.04 (s, 2H), 6.93-7.01 (m, 3H), 7.59 (s, 1H), 8.26 (s, 1H), 8.97 (s, 1H), 11.28 (br s, 1H); Mass Spectrum: $M+H^+$ 490.

The 7-(4-chlorobutoxy)-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline hydrochloride salt used as a starting material was prepared as follows :-

A mixture of 4-chloro-7-(4-chlorobutoxy)-3-cyano-6-methoxyquinoline (J. Medicinal Chemistry, 2001, 44, 3965-3977; 1.0 g), 2,3-methylenedioxyaniline (0.46 g) and 1-propanol (25 ml) was stirred and heated to 100°C for 5 hours. The mixture was allowed to cool to ambient temperature and the precipitate was isolated and washed in turn with cold 1-propanol (25 ml) and diethyl ether (2 x 25 ml). The solid was dried under vacuum. There was thus obtained the required starting material (1.3 g); NMR Spectrum: ($DMSOd_6$) 1.9-1.98 (m, 4H), 3.74 (t, 2H), 4.23 (t, 2H), 6.04 (s, 2H), 6.94-7.01 (m, 3H), 7.5 (s, 1H), 8.18 (s, 1H), 8.96 (s, 1H), 11.11 (br s, 1H).

[28] The reactants were 7-(4-chlorobutoxy)-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline hydrochloride salt and 1-acetylpiperazine. Moreover, 1-propanol was used in place of DMF and the reaction mixture was heated to 90°C for 18 hours. The reaction product was dissolved in ethyl acetate and a solution of hydrogen chloride in diethyl ether (1M, 1 ml) was added. The resultant solid was isolated and washed with diethyl ether. Thereby, the product was obtained as a dihydrochloride salt and gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 1.88-1.95 (m, 4H), 2.03 (s, 3H), 2.8-3.22 (m, 5H), 3.4-3.64 (m, 3H), 3.91-4.06 (m, 4H), 4.22 (br s, 2H), 4.37-4.42 (m, 1H), 6.05 (s, 2H), 6.92-7.02 (m, 3H), 7.62 (s, 1H), 8.31 (s, 1H), 9.01 (s, 1H), 11.21 (br s, 1H), 11.43 (br s, 1H); Mass Spectrum: $M+H^+$ 518.

[29] 1,2,3,6-Tetrahydropyridine was used as the heterocycle reactant. Moreover, 2-methoxyethanol was used in place of DMF and the reaction mixture was heated to 90°C for 5 hours. The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 1.97 (m, 2H), 2.08 (s, 2H), 2.55 (m, 4H), 2.95 (s, 2H), 3.95 (s, 3H), 4.21 (t, 2H), 5.68 (m, 2H), 5.99 (s, 2H), 6.87 (m, 2H), 6.92 (t, 1H), 7.32 (s, 1H), 7.78 (s, 1H), 8.42 (s, 1H), 9.49 (s, 1H); Mass Spectrum: $M+H^+$ 459.

[30] 2-Methoxyethanol was used in place of DMF and the reaction mixture was heated to 100°C for 2 hours. The product gave the following characterising data; NMR Spectrum: ($CDCl_3$) 1.74 (m, 2H), 1.95 (m, 2H), 2.18 (m, 2H), 2.48 (t, 2H), 2.56 (t, 2H), 2.97 (t, 2H), 3.7 (s, 3H), 4.18 (t, 2H), 5.66 (m, 1H), 5.75 (m, 1H), 5.93 (s, 2H), 6.64 (d, 1H), 6.73 (d, 1H), 6.82 (t, 1H), 6.9 (s, 1H), 7.02 (s, 1H), 7.33 (s, 1H), 8.6 (s, 1H); Mass Spectrum: $M+H^+$ 473.

[31] 2,5-Dimethylpyrrole was used as the heterocycle reactant. Moreover, 2-methoxyethanol was used in place of DMF and the reaction mixture was heated to 95°C for 12 hours. The product gave the following characterising data; NMR Spectrum: ($CDCl_3$) 2.16-2.32 (m, 2H), 2.23 (s, 6H), 3.72 (s, 3H), 4.04 (t, 2H), 4.14 (t , 2H), 5.77 (s, 2H), 5.95 (s, 2H), 6.63 (m, 2H), 6.76 (d ,1H), 6.86 (t, 1H), 6.98 (s, 1H), 7.33 (s, 1H), 8.61 (s, 1H); Mass Spectrum: $M+H^+$ 471.

[32] 2,5-Dimethyl-3-pyrroline was used as the heterocycle reactant, the material being obtained commercially as a mixture of cis and trans isomers based on the stereochemical relationship of the methyl groups. 2-Methoxyethanol was used in place of DMF and the reaction mixture was heated to 95°C for 12 hours. Two isomeric products were obtained, based on the stereochemical relationship of the methyl groups. The isomers were separated during the chromatographic purification step and gave the following characterising data;

Isomer 1: NMR Spectrum: ($CDCl_3$) 1.16 (d, 6H), 2.08-2.18 (m, 2H), 2.91 (t, 2H), 3.61 (m, 2H), 3.72 (s, 3H), 4.27 (t, 2H), 5.55 (s, 2H), 5.92 (s, 2H), 6.63 (m, 2H), 6.73 (d, 1H), 6.86 (t, 1H), 6.98 (s, 1H), 7.39 (s, 1H), 8.61 (s, 1H); Mass Spectrum: $M-H^-$ 471.

Isomer 2: NMR Spectrum: ($CDCl_3$) 1.16 (br s, 6H), 2.08-2.13 (br s, 2H), 2.91 (br s, 2H), 3.72 (s, 3H), 3.9 (br s, 2H), 4.27 (m, 2H), 5.72 (s, 2H), 5.95 (s, 2H), 6.62-6.88 (m, 4H), 7.02 (s, 1H), 7.38 (s, 1H), 8.6 (s, 1H); Mass Spectrum: $M-H^-$ 471.

[33] The reactants were 7-[(2R)-3-chloro-2-fluoropropoxy]-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline and 1,2,3,6-tetrahydropyridine. Moreover, 2-methoxyethanol was used in place of DMF and the reaction mixture was heated to 100°C for 12 hours. The reaction product was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and a 7M solution of ammonia in methanol as eluent. The material so obtained was dissolved in ethyl acetate and a solution of hydrogen chloride in diethyl ether (1M, 1 ml) was added. The resultant solid was washed with diethyl ether to give the required product as a dihydrochloride salt which gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 3.18-3.96 (m, 8H), 4.05 (s, 3H), 4.46-4.63 (m, 2H), 5.68-6.0 (m, 3H), 6.07 (s, 2H), 6.92-7.02 (m, 3H), 7.62 (s, 1H), 8.33 (s, 1H), 8.97 (s, 1H), 11.28 (br s, 2H); Mass Spectrum: $M+H^+$ 477.

The 7-[(2R)-3-chloro-2-fluoropropoxy]-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline used as a starting material was prepared as follows :-

Carbon tetrachloride (0.26 ml) was added to a mixture of (2S)-3-benzyloxy-2-fluoropropan-1-ol (J. Org. Chem., 1997, 62, 7546-7547; 0.44 g), triphenylphosphine (0.69 g) and methylene chloride (10 ml) and the mixture was stirred at ambient temperature for 12 hours. A further portion of triphenylphosphine (0.3 g) was added and the mixture was stirred at ambient temperature for 5 hours. The mixture was purified by column chromatography on silica using a 9:1 mixture of hexane and ethyl acetate as eluent. There was thus obtained (2R)-3-benzyloxy-2-fluoropropyl chloride as an oil (0.4 g); NMR Spectrum: ($CDCl_3$) 3.66-3.81 (m, 4H), 4.55-4.62 (m, 2H), 4.71-4.87 (m, 1H), 7.28-7.38 (m, 5H).

A solution of (2R)-3-benzyloxy-2-fluoropropyl chloride (0.65 g) in methylene chloride (15 ml) was cooled to –78°C and boron trichloride (1M solution in methylene chloride; 4.8 ml) was added. The mixture was stirred at –78°C for 3 hours. The mixture was poured into a 1N aqueous hydrochloric acid solution (50 ml) and extracted with methylene chloride. The organic phase was dried over magnesium sulphate and concentrated by evaporation to a

volume of approximately 20 ml. There was thus obtained a solution of (2R)-3-chloro-2-fluoropropan-1-ol which was used without further purification.

Triphenylphosphine (1 g) and 4-chloro-3-cyano-7-hydroxy-6-methoxyquinoline (0.83 g) were added in turn to the solution of (2R)-3-chloro-2-fluoropropan-1-ol in methylene chloride. Diisopropyl azodicarboxylate (0.6 ml) was added and the mixture was stirred at ambient temperature for 12 hours. The mixture was poured into water and the organic layer was separated, washed with a saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated. The crude product so obtained was purified by column chromatography on silica using a 1:1 mixture of isohexane and ethyl acetate as eluent. There was thus obtained 4-chloro-7-[(2R)-3-chloro-2-fluoropropoxy]-3-cyano-6-methoxyquinoline (0.66 g); NMR Spectrum: ($DMSOd_6$) 4.02 (s, 3H), 3.9-4.12 (m, 2H), 4.42-4.64 (m, 2H), 5.09-5.31 (m, 1H), 7.47 (s, 1H), 7.6 (s, 1H), 8.44 (br s, 1H), 8.98 (s, 1H).

A mixture of 4-chloro-7-[(2R)-3-chloro-2-fluoropropoxy]-3-cyano-6-methoxyquinoline (0.27 g), 2,3-methylenedioxyaniline (0.13 g) and 1-propanol was stirred and heated to 90°C for 18 hours. The mixture was allowed to cool to ambient temperature. The precipitate was isolated and washed in turn with cold 1-propanol (10 ml) and with diethyl ether (2 x 10 ml). There was thus obtained 7-[(2R)-3-chloro-2-fluoropropoxy]-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline (0.26 g); NMR Spectrum: ($DMSOd_6$) 4.01 (s, 3H), 3.93-4.14 (m, 2H), 4.38-4.58 (m, 2H), 5.14-5.32 (m, 1H), 6.05 (s, 2H), 6.92-7.01 (m, 3H), 7.52 (s, 1H), 8.2 (s, 1H), 8.95 (s, 1H), 11.09 (br s, 1H); Mass Spectrum: $M+H^+$ 430.

[34] The reactants were 7-[(2R)-3-chloro-2-fluoropropoxy]-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline and morpholine. Moreover, 2-methoxyethanol was used in place of DMF and the reaction mixture was heated to 100°C for 12 hours. The reaction product was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and a 7M solution of ammonia in methanol as eluent. The material so obtained was dissolved in ethyl acetate and a solution of hydrogen chloride in diethyl ether (1M, 1 ml) was added. The resultant solid was washed with diethyl ether to give the required product as a dihydrochloride salt which gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 3.25-3.37 (m, 4H), 3.52-3.72 (m, 2H), 3.89-3.97 (m, 4H), 4.02 (s, 3H), 4.40-4.65 (m, 2H), 5.55-5.81 (m, 1H), 6.0 (s, 2H), 6.88-6.96 (m, 3H), 7.59 (s, 1H), 8.15 (s, 1H), 8.69 (s, 1H); Mass Spectrum: $M+H^+$ 481.

[35] The reactants were 7-(3-chloropropoxy)-3-cyano-6-methoxy-4-[4-(2-methoxyethyl)-2,3-methylenedioxyanilino]quinoline (described as Example 10(26)

hereinafter) and morpholine. The reaction product was treated with a 1M solution of hydrogen chloride in diethyl ether. The resultant solid was washed with diethyl ether to give the required product as a dihydrochloride salt which gave the following characterising data; Mass Spectrum: $M-H^-$ 519.

Example 5

3-cyano-7-hydroxy-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline

A mixture of 4-chloro-3-cyano-7-hydroxy-6-methoxyquinoline (5 g), 2,3-methylenedioxyaniline (3.07 g) and propanol (100 ml) was stirred and heated to 115°C for 18 hours. The resultant precipitate was isolated, washed in turn with propanol and diethyl ether and dried under vacuum. There was thus obtained the title compound (5.51 g); NMR Spectrum: ($DMSOd_6$) 3.99 (s, 3H), 6.06 (s, 2H), 6.93-7.0 (m, 3H), 7.48 (s, 1H), 8.16 (s, 1H), 8.94 (s, 1H); Mass Spectrum: $M+H^+$ 336.

Example 6

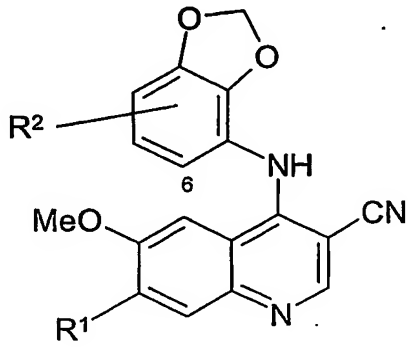
3-cyano-6-methoxy-7-(2-methoxyethoxy)-4-(2,3-methylenedioxyanilino)quinoline

A mixture of 3-cyano-7-hydroxy-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline (0.2 g), 2-bromoethyl methyl ether (0.09 g), potassium carbonate (0.22 g) and DMA (5 ml) was stirred and heated to 60°C for 3 hours. The mixture was evaporated and the residue was partitioned between ethyl acetate and water. The organic phase was washed in turn with water, a 2N aqueous sodium hydroxide solution and brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and ethyl acetate as eluent. The material so obtained was dissolved in diethyl ether and a solution of hydrogen chloride in diethyl ether (1M, 2 ml) was added. The resultant solid was washed with diethyl ether. There was thus obtained the title compound solid as a mono-hydrochloride salt (0.135 g); NMR Spectrum: ($DMSOd_6$) 3.32 (s, 3H), 3.76 (m, 2H), 3.99 (s, 3H), 4.28 (m, 2H), 6.04 (s, 2H), 6.96 (m, 3H), 7.49 (s, 1H), 8.15 (s, 1H), 8.94 (s, 1H); Mass Spectrum: $M-H^-$ 392.

Example 7

Using an analogous procedure to that described in Example 6, the appropriate 3-cyano-7-hydroxyquinoline was reacted with the appropriate alkyl halide to give the compounds described in Table II.

Table II



Compound No. & Note	R^1	R^2
[1]	2-(2-hydroxyethoxy)ethoxy	hydrogen
[2]	2-hydroxyethoxy	hydrogen

Notes

[1] 2-(2-Chloroethoxy)ethanol was used as the alkyl halide and the reaction mixture was heated to 60°C for 18 hours. Hoever, unlike in Example 6, the product was not treated with a solution of hydrogen chloride in diethyl ether and, accordingly, the product was obtained as a free base. The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 3.51 (m, 4H), 3.81 (m, 2H), 3.93 (s, 3H), 4.28 (m, 2H), 4.58 (m, 1H), 5.97 (s, 2H), 6.8-6.91 (m, 3H), 7.32 (s, 1H), 7.77 (s, 1H), 8.41 (s, 1H), 9.5 (s, 1H); Mass Spectrum: $M+H^+$ 424.

[2] 2-Chloroethanol was used as the alkyl halide. The product was treated with a solution of hydrogen chloride in diethyl ether. The mono-hydrochloride salt so obtained gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 3.81 (t, 2H), 3.99 (s, 3H), 4.2 (t, 2H), 6.04 (s, 2H), 6.96 (m, 3H), 7.49 (s, 1H), 8.15 (s, 1H), 8.94 (s, 1H); Mass Spectrum: $M+H^+$ 380.

Example 8

7-(3-bromopropoxy)-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline

Diisopropyl azodicarboxylate (0.29 g) was added dropwise to a stirred suspension of 3-cyano-7-hydroxy-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline (0.4 g), 3-bromopropanol (0.25 g), triphenyl phosphine (0.44 g) and methylene chloride (15 ml). The mixture was stirred at ambient temperature for 18 hours. The mixture was evaporated and the residue was purified by column chromatography on silica eluting with increasingly polar mixtures of methylene chloride and ethyl acetate as eluent. The gum so obtained was triturated under diethyl ether. There was thus obtained the title compound as a solid (0.4 g); NMR Spectrum: ($DMSOd_6$) 2.32 (m, 2H), 3.68 (t, 2H), 3.94 (s, 3H), 4.26 (t, 2H), 5.98 (s, 2H), 6.8-6.92 (m, 3H), 7.32 (s, 1H), 7.78 (s, 1H), 8.42 (s, 1H); Mass Spectrum: $M+H^+$ 458.

Example 9

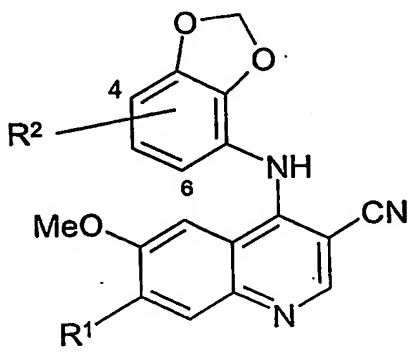
7-(2-bromoethoxy)-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline

Using an analogous procedure to that described in Example 8, 3-cyano-7-hydroxy-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline was reacted with 2-bromoethanol to give the title compound in 82% yield; NMR Spectrum: ($DMSOd_6$) 3.88 (t, 2H), 3.94 (s, 3H), 4.51 (t, 2H), 5.96 (s, 2H), 6.8-6.93 (m, 3H), 7.34 (s, 1H), 7.8 (s, 1H), 8.42 (s, 1H), 9.53 (s, 1H); Mass Spectrum: $M+H^+$ 444.

Example 10

Using an analogous procedure to that described in Example 1, the appropriate 4-chloro-3-cyanoquinoline was reacted with the appropriate 2,3-methylenedioxyaniline to give the compounds described in Table III. Unless otherwise stated, each product was obtained as a free base.

Table III



Compound No. & Note	R^1	R^2
[1]	methoxy	hydrogen
[2]	methoxy	6-chloro
[3]	methoxy	6-bromo
[4]	3-(4-methylpiperazin-1-yl)propoxy	6-fluoro
[5]	3-(4-methylpiperazin-1-yl)propoxy	5-bromo
[6]	3-(4-methylpiperazin-1-yl)propoxy	4-bromo
[7]	3-morpholinopropoxy	hydrogen
[8]	(2S)-2-fluoro-3-(4-methylpiperazin-1-yl)propoxy	hydrogen
[9]	methoxy	4-iodo
[10]	methoxy	4-iodo-6-chloro
[11]	methoxy	6-iodo
[12]	methoxy	4-bromo
[13]	methoxy	5-bromo
[14]	methoxy	5-fluoro
[15]	methoxy	4-hydroxymethyl
[16]	methoxy	4-methyl
[17]	methoxy	4-benzyl
[18]	methoxy	4-methylthio
[19]	3-(4-methylpiperazin-1-yl)propoxy	4-iodo
[20]	methoxy	4-(2-methoxyethyl)
[21]	methoxy	4-morpholinomethyl
[22]	methoxy	4-dimethylaminomethyl
[23]	methoxy	4-oxazol-5-yl
[24]	3-(4-methylpiperazin-1-yl)propoxy	4-(2-methoxyethyl)
[25]	3-(1,1-dioxotetrahydro-4H-thiazin-4-yl)propoxy	4-(2-methoxyethyl)
[26]	3-chloropropoxy	4-(2-methoxyethyl)
[27]	methoxy	5-methyl
[28]	methoxy	5-methoxymethyl

Notes

[1] 4-Chloro-3-cyano-6,7-dimethoxyquinoline (International Patent Application WO 98/43960) was used as a starting material. The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 4.02 (s, 3H), 4.05 (s, 3H), 6.12 (s, 2H), 7.0-7.1 (m, 3H), 7.45 (s, 1H), 8.12 (s, 1H), 9.15 (s, 1H); Mass Spectrum: $M+H^+$ 350.

[2] The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 4.04 (s, 3H), 4.06 (s, 3H), 6.2 (d, 2H), 7.12 (d, 1H), 7.2 (d, 1H), 7.5 (s,1H), 8.15 (s, 1H), 9.2 (s, 1H); Mass Spectrum: $M+H^+$ 384 and 386.

[3] The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 4.03 (s, 3H), 4.05 (s, 3H), 6.2 (s, 2H), 7.1 (d, 1H), 7.35 (d, 1H), 7.48 (s, 1H), 8.15 (s, 1H), 9.18 (s, 1H); Mass Spectrum: $M+H^+$ 428 and 430.

The 6-bromo-2,3-methylenedioxyaniline used as a starting material was prepared from 5-bromo-1,3-benzodioxole (Aldrich Chemical Company) using analogous procedures to those described in the portion of Example 1 above that is concerned with the preparation of 6-chloro-2,3-methylenedioxyaniline. There were thus obtained in turn :-

5-bromo-1,3-benzodioxole-4-carboxylic acid; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 6.15 (s, 2H), 6.95 (d, 1H), 7.1 (d, 1H); Mass Spectrum: $[M-H]^-$ 243;

tert-butyl N-(5-bromo-1,3-benzodioxol-4-yl)carbamate; NMR Spectrum: ($DMSOd_6$) 1.45 (s, 9H), 6.1 (s, 2H), 6.80 (d, 1H), 7.1 (d, 1H), 8.70 (s, 1H); and

6-bromo-2,3-methylenedioxyaniline; NMR Spectrum: ($DMSOd_6$) 5.05 (s, 2H), 6.0 (s, 2H), 6.25 (d, 1H), 6.9 (d, 1H); Mass Spectrum: $M+H^+$ 216 and 218.

[4] The reaction product was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and a saturated methanolic ammonia solution as eluent. The material so obtained was dissolved in diethyl ether and a solution of hydrogen chloride in diethyl ether (1M, 2 ml) was added. The resultant solid was washed with diethyl ether to give the required product as a dihydrochloride salt which gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.12 (m, 2H), 2.85 (s, 3H), 3.27-3.88 (m, 10H), 4.0 (s, 3H), 4.32 (t, 2H), 6.11 (s, 2H), 6.87 (m, 1H), 7.0 (m, 1H), 7.52 (s, 1H), 8.16 (s, 1H), 8.97 (s, 1H); Mass Spectrum: $M+H^+$ 494.

The 6-fluoro-2,3-methylenedioxyaniline used as a starting material was prepared as follows :-

A mixture of diisopropylamine (4.92 ml) and THF (100 ml) was cooled to -78°C and n-butyllithium (2.5 M in THF, 14 ml) was added dropwise. The mixture was stirred at -70°C

for 30 minutes. 4-Fluoro-1,2-dimethoxybenzene (5 g) was added dropwise and the reaction mixture was stirred at -70°C for 20 minutes. Dry carbon dioxide gas was bubbled into the reaction mixture for 15 minutes. The resultant reaction mixture was allowed to warm to ambient temperature and was stirred for a further hour. Water was added and the organic solvent was evaporated. The residue was acidified to pH2 by the addition of 2N aqueous hydrochloric acid solution and the mixture was extracted with a mixture of diethyl ether and ethyl acetate. The organic phase was dried over magnesium sulphate and evaporated. The solid so obtained was washed with pentane and dried under vacuum. There was thus obtained 6-fluoro-2,3-dimethoxybenzoic acid (3.4 g); NMR Spectrum: ($DMSOd_6$) 3.8 (s, 3H), 3.85 (s, 3H), 7.0 (t, 1H), 7.15 (m, 1H).

A mixture of 6-fluoro-2,3-dimethoxybenzoic acid (14 g), concentrated aqueous hydrobromic acid (47%, 230 ml) and acetic acid (200 ml) was stirred and heated to 140°C for 1 hour. The mixture was cooled to ambient temperature and partitioned between ethyl acetate and water. The organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated to give 6-fluoro-2,3-dihydroxybenzoic acid (9.3 g); NMR Spectrum: ($DMSOd_6$) 6.55 (t, 1H), 6.9 (m, 1H), 9.3 (br s, 2H).

Thionyl chloride (6 ml) was added dropwise to a solution of 6-fluoro-2,3-dihydroxybenzoic acid (9.3 g) in methanol (80 ml) that had been cooled to 0°C. The resultant mixture was stirred and heated to 60°C for 24 hours. The mixture was evaporated and the residue was partitionned between ethyl acetate and a saturated aqueous sodium bicarbonate solution. The organic phase was washed with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica eluting with increasingly polar mixtures of petroleum ether (b.p. 40-60°C) and ethyl acetate as eluent. There was thus obtained methyl 6-fluoro-2,3-dihydroxybenzoate (7.2 g); NMR Spectrum: ($CDCl_3$) 4.0 (s, 3H), 5.45 (s, 1H), 6.5 (t, 1H), 7.0 (m, 1H).

Potassium fluoride (11.2 g) was added to a solution of methyl 6-fluoro-2,3-dihydroxybenzoate (7.2 g) in DMF (110 ml) and the mixture was stirred and heated to 100°C for 15 minutes. Diiodomethane (3.43 ml) was added and the mixture was stirred and heated to 100°C for 75 mnutes. The mixture was cooled to ambient temperature and partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over magnesium sulphate and evaporated. The resultant residue was purified by colum chromatography on silica using increasingly polar mixtures of petroleum ether (b.p. 40-60°C) and ethyl acetate as eluent. There was thus obtained methyl 6-fluoro-

2,3-methylenedioxybenzoate (4.5 g); NMR Spectrum: ($DMSOd_6$) 3.85 (s, 3H), 6.2 (s, 2H), 6.8 (m, 1H), 7.15 (m, 1H).

A suspension of the material so obtained, a 2N aqueous potassium hydroxide solution (23 ml) and methanol (60 ml) was stirred at ambient temperature for 3 hours. The mixture was evaporated and the residue was dissolved in water and the solution was acidified to pH2 by the addition of 6N aqueous hydrochloric acid. The resultant precipitate was isolated, washed with water and dried overnight under vacuum over phosphorus pentoxide. There was thus obtained 6-fluoro-2,3-methylenedioxybenzoic acid (4 g); NMR Spectrum: ($DMSOd_6$) 6.15 (s, 2H), 6.75 (m, 1H), 7.05 (m, 1H).

The material so obtained was dissolved in 1,4-dioxane (60 ml) and anhydrous tert-butanol (17 ml), diphenylphosphoryl azide (5 ml) and triethylamine (3.8 ml) were added in turn. The resultant mixture was stirred and heated to 100°C for 4.5 hours. The mixture was cooled to ambient temperature and filtered. The filtrate was evaporated and the resultant residue was partitioned between ethyl acetate and a 5% aqueous citric acid solution. The organic phase was washed in turn with water, a saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and evaporated. There was thus obtained tert-butyl N-(5-fluoro-1,3-benzodioxol-4-yl)carbamate (4.5 g); NMR Spectrum: ($CDCl_3$) 1.5 (s, 9H), 5.95 (br s, 1H), 6.0 (s, 2H), 6.55 (m, 2H).

A mixture of a portion (2.5 g) of the material so obtained, trifluoroacetic acid (15 ml) and methylene chloride (55 ml) was stirred at ambient temperature for 3.5 hours. The solvent was evaporated and the residue was partitioned between ethyl acetate and a saturated aqueous sodium bicarbonate solution. The organic phase was washed with brine, dried over magnesium sulphate and evaporated. There was thus obtained 6-fluoro-2,3-methylenedioxyaniline (1.1 g); NMR Spectrum: ($DMSOd_6$) 5.0 (br s, 2H), 5.95 (s, 2H), 6.15 (m, 1H), 6.55 (m, 1H).

[5] The product gave the following characterising data; NMR Spectrum: ($CDCl_3$) 2.1 (m, 2H), 2.28 (s, 3H), 2.4-2.6 (m, 8H), 2.55 (t, 2H), 3.78 (s, 3H), 4.24 (t, 2H), 5.97 (s, 2H), 6.64 (s, 1H), 6.72 (s, 1H), 6.97 (s, 1H), 7.4 (s, 1H), 8.63 (s, 1H); Mass Spectrum: $M+H^+$ 554 and 556.

The 5-bromo-2,3-methylenedioxyaniline used as a starting material was prepared as follows :-

A mixture of 6-bromo-1,3-benzodioxole-4-carboxylic acid [Khim. Geterotsikl. Soedin 1979, 9, 1183-8 (Chemical Abstracts 92, 94280); 0.92 g], diphenylphosphoryl azide (1.08 g),

tert-butanol (3 ml), triethylamine (0.34 g) and toluene (15 ml) were stirred and heated at 100°C for 4 hours. The resultant mixture was evaporated and the residue was partitioned between methyl tert-butyl ether and a 5% aqueous citric acid solution. The organic phase was washed with water and a saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate and evaporated. The residual oil was purified by column chromatography on silica using a 5:1 mixture of isohexane and ethyl acetate as eluent. There was thus obtained tert-butyl N-(6-bromo-1,3-benzodioxol-4-yl)carbamate (0.6 g); NMR Spectrum: ($CDCl_3$) 1.52 (s, 9H), 5.95 (s, 2H), 6.39 (br s, 1H), 6.7 (d, 1H), 7.73 (br s, 1H).

A mixture of the material so obtained, trifluoroacetic acid (3 ml) and methylene chloride (8 ml) was stirred at ambient temperature for 1 hour. The solvent was evaporated and the residue was partitioned between methyl tert-butyl ether and a saturated aqueous sodium bicarbonate solution. The organic phase was washed with a saturated brine solution, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 4:1 mixture of isohexane and ethyl acetate as eluent. There was thus obtained 5-bromo-2,3-methylenedioxyaniline (0.318 g) as a colourless solid; NMR Spectrum: ($CDCl_3$) 3.6 (br s, 2H), 5.92 (s, 2H), 6.27 (m, 2H).

[6] The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 1.96 (m, 2H), 2.15 (s, 3H), 2.25-2.5 (m, 10H), 3.94 (s, 3H), 4.18 (t, 2H), 6.09 (s, 2H), 6.84 (d, 1H), 7.09 (d, 1H), 7.3 (s, 1H), 7.74 (s, 1H), 8.43 (s, 1H), 9.52 (s, 1H); Mass Spectrum: $M+H^+$ 554 and 556.

[7] 4-Chloro-3-cyano-6-methoxy-7-(3-morpholinopropoxy)quinoline (International Patent Application WO 00/68201, page 52) was used as a starting material. The reaction product was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. The material so obtained was dissolved in diethyl ether and a solution of hydrogen chloride in diethyl ether (1M) was added. The resultant solid was washed with diethyl ether to give the required product as a dihydrochloride salt which gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.26–2.37 (m, 2H), 3.04–3.16 (m, 2H), 3.26–3.34 (t, 2H), 3.45–3.55 (m, 2H), 3.72–3.87 (m, 2H), 3.94–4.03 (m, 5H), 4.31 (t, 2H), 6.04 (s, 2H), 6.94–6.99 (m, 3H), 7.49 (s, 1H), 8.14 (s, 1H), 8.96 (s, 1H); Mass Spectrum: $M-H^-$ 461.

[8] The reaction mixture was stirred at 0°C for 2 hours. The reaction product was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and a 7M solution of ammonia in methanol as eluent. The material so obtained was dissolved

in ethyl acetate and a solution of hydrogen chloride in diethyl ether (1M, 1 ml) was added. The resultant solid was washed with diethyl ether to give the required product as a dihydrochloride salt which gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 2.81 (s, 3H), 3.0-3.63 (m, 10H), 4.05 (s, 3H), 4.42-4.57 (m, 2H), 5.39-5.52 (m, 1H), 6.08 (s, 2H), 6.96-7.1 (m, 3H), 7.61 (s, 1H), 8.29 (s, 1H), 9.03 (s, 1H), 11.30 (br s, 1H); Mass Spectrum: $M+H^+$ 494.

The 4-chloro-3-cyano-7-[(2S)-2-fluoro-3-(4-methylpiperazin-1-yl)propoxy]-6-methoxyquinoline used as a starting material was prepared as follows :-

A mixture of (2R)-3-benzyloxy-2-fluoropropyl chloride (0.4 g), 1-methylpiperazine (2.2 ml) and 2-methoxyethanol (5 ml) was stirred and heated to 80°C for 12 hours and then to 110°C for 6 hours. The resultant mixture was poured into a mixture of water (50 ml) and a saturated aqueous sodium chloride solution (50 ml) and extracted with ethyl acetate (3 x 25 ml). The organic extracts were dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and a 7N solution of ammonia in methanol as eluent. There was thus obtained benzyl (2S)-2-fluoro-3-(4-methylpiperazin-1-yl)propyl ether as an oil (0.27 g); NMR Spectrum: ($CDCl_3$) 2.28 (s, 3H), 2.33-2.75 (m, 10H), 3.61-3.68 (m, 2H), 4.58 (s, 2H), 4.73-4.91 (m, 1H), 7.28-7.38 (m, 5H).

The material so obtained was dissolved in methanol (10 ml) and 10% palladium-on-carbon (0.77 g) and ammonium formate (0.65 g) were added and the mixture was heated to reflux for 5 hours. A further portion of ammonium formate (0.7 g) was added and the mixture was heated to reflux for 12 hours. The mixture was allowed to cool to ambient temperature and filtered. The filtrate was evaporated and the crude product so obtained was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and a 7N solution of ammonia in methanol as eluent. There was thus obtained (2S)-2-fluoro-3-(4-methylpiperazin-1-yl)propan-1-ol as an oil (0.082 g); NMR Spectrum: ($CDCl_3$) 2.28 (s, 3H), 2.3-2.71 (m, 8H), 2.74 (d, 1H), 2.79 (m, 1H), 3.84 (t, 1H), 3.89 (d, 1H), 4.59-4.75 (m, 1H); Mass Spectrum: $M+H^+$ 177.

Using an analogous procedure to that described in Example 8, (2S)-2-fluoro-3-(4-methylpiperazin-1-yl)propan-1-ol (0.082 g) was reacted with 4-chloro-3-cyano-7-hydroxy-6-methoxyquinoline (0.14 g) to give 4-chloro-3-cyano-7-[(2S)-2-fluoro-3-(4-methylpiperazin-1-yl)propoxy]-6-methoxyquinoline.

[9] The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 3.77 (s, 3H), 3.81 (s, 3H), 5.88 (s, 2H), 6.3 (d, 1H), 6.87 (d, 1H), 6.93 (s, 1H), 7.7 (s, 1H), 7.83 (s, 1H); Mass Spectrum: $M+H^+$ 476.

The 4-iodo-2,3-methylenedioxyaniline used as a starting material was prepared as follows :-

Benzyltrimethylammonium dichloroiodate (2.8 g) was added portionwise during 10 minutes to a stirred mixture of 2,3-methylenedioxyaniline (1 g), calcium carbonate (0.95 g), methanol (5 ml) and methylene chloride (10 ml). The reaction mixture was stirred at ambient temperature for 1.5 hours. The resultant mixture was diluted with water and extracted with methylene chloride. The organic phase was washed with water and with a saturated brine solution, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of isohexane and methylene chloride as eluent. There was thus obtained 4-iodo-2,3-methylenedioxyaniline as a solid (1.1 g); NMR Spectrum: ($DMSOd_6$) 5.04 (br s, 2H), 5.94 (s, 2H), 6.13 (d, 1H), 6.8 (d, 1H).

[10] The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 4.0 (s, 6H), 6.18 (s, 2H), 7.38 (s, 1H), 7.48 (s, 1H), 7.88 (s, 1H), 8.44 (s, 1H), 9.45 (s, 1H); Mass Spectrum: $M+H^+$ 510.

The 6-chloro-4-iodo-2,3-methylenedioxyaniline used as a starting material was prepared by the reaction of 6-chloro-2,3-methylenedioxyaniline and benzyltrimethylammonium dichloroiodate in an analogous manner to that described in Note [9] immediately above. The material so obtained gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 6.04 (s, 2H), 7.0 (s, 1H).

[11] The required 6-iodo-2,3-methylenedioxyanilino product was obtained as the major portion of a 4:1 mixture, the minor portion being the 4,6-diiodo-2,3-methylenedioxyanilino compound. The mixture of materials gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 3.98 (s, 6H), 6.09 (s, 2H), 6.87 (d, 1H), 7.34 (s, 1H), 7.47 (d, 1H), 7.89 (s, 1H), 8.41 (s, 1H), 9.42 (s, 1H); Mass Spectrum: $M+H^+$ 476 and 602.

The 4:1 mixture of 6-iodo-2,3-methylenedioxyaniline and 4,6-diiodo-2,3-methylenedioxyaniline used as a starting material was prepared as follows :-

Benzyltrimethylammonium dichloroiodate (12 g) was added portionwise during 20 minutes to a stirred mixture of 2,3-methylenedioxyaniline (4 g), calcium carbonate (3.77 g), methanol (20 ml) and methylene chloride (40 ml). The reaction mixture was stirred

at ambient temperature for 1 hour. The resultant mixture was diluted with water and extracted with methylene chloride. The organic phase was washed with water and with a saturated brine solution, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of isohexane and methylene chloride as eluent. There was thus obtained 4-iodo-2,3-methylenedioxyaniline (2.7 g) and a 4:1 mixture (1.6 g) of 4-iodo-2,3-methylenedioxyaniline and 4,6-diiodo-2,3-methylenedioxyaniline; NMR Spectrum: ($DMSOd_6$) 6.03 (s, 2H), 7.33 (s, 1H).

[12] The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 3.96 (s, 3H), 3.97 (s, 3H), 6.08 (s, 2H), 6.83 (s, 1H), 7.08 (s, 1H), 7.3 (s, 1H), 7.75 (s, 1H), 8.43 (s, 1H), 9.5 (s, 1H); Mass Spectrum: $M+H^+$ 428 and 430.

[13] The product gave the following characterising data; NMR Spectrum: ($CDCl_3$) 3.83 (s, 3H), 4.05 (s, 3H), 5.98 (s, 2H), 6.76 (d, 1H), 6.84 (d, 1H), 6.9 (br s, 1H), 7.06 (s, 1H), 7.39 (s, 1H), 8.64 (s, 1H); Mass Spectrum: $M+H^+$ 428 and 430.

[14] The product gave the following characterising data; NMR Spectrum: ($CDCl_3$) 3.81 (s, 3H), 4.05 (s, 3H), 5.96 (s, 2H), 6.3 (m, 1H), 6.5 (m, 1H), 6.64 (br s, 1H), 7.01 (s, 1H), 7.4 (s, 1H), 8.65 (s, 1H); Mass Spectrum: $M+H^+$ 368.

The 5-fluoro-2,3-methylenedioxyaniline used as a starting material was prepared as follows :-

A mixture of 5-bromo-2,3-methylenedioxyaniline (2.0 g), 1,2-bis(chlorodimethylsilyl)ethane (2.09 g), triethylamine (1.96 g) and methylene dichloride (50 ml) was stirred at ambient temperature for 88 hours. The resultant mixture was washed with a 5% aqueous sodium dihydrogen phosphate solution, dried over magnesium sulphate and evaporated. The oil so obtained was purified by column chromatography on neutral alumina using isohexane as eluent. There was thus obtained N-(5-bromo-2,3-methylenedioxyphenyl)-2,2,5,5-tetramethyl-1,2,5-azadisilolidine as an oil (2.4 g); NMR Spectrum: ($CDCl_3$) 0.13 (s, 12H), 0.86 (s, 4H), 5.87 (s, 2H), 6.59 (d, 1H), 6.67 (d, 1H).

n-Butyllithium (1.6M in THF, 1.1 ml) was added to a solution of N-(5-bromo-2,3-methylenedioxyphenyl)-2,2,5,5-tetramethyl-1,2,5-azadisilolidine (0.6 g) in THF (10 ml) that had been cooled to -70°C and the mixture was stirred at -70°C for 1 hour. A solution of N-fluorobenzenesulphonimide (1.0 g) in THF (3 ml) was added and the mixture was allowed to warm to 0°C over 3 hours. The mixture was stirred at 0°C for a further hour. The mixture was poured into a cooled 1N aqueous hydrochloric acid solution and stirred for 5 minutes and extracted with diethyl ether. The aqueous phase was basified with a 40% aqueous sodium

hydroxide solution and extracted with diethyl ether. The organic phase was washed with a saturated brine solution, dried over magnesium sulphate and evaporated. There was thus obtained 5-fluoro-2,3-methylenedioxyaniline as an oil (0.12 g) which was used without further purification.

[15] The reactants were 4-chloro-3-cyano-6,7-dimethoxyquinoline (0.082 g) and 4-tert-butyldimethylsilyloxymethyl-2,3-methylenedioxyaniline (0.1 g) and the initial product was 4-(4-tert-butyldimethylsilyloxymethyl-2,3-methylenedioxyanilino)-3-cyano-6,7-dimethoxyquinoline (0.115 g) which gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 0.1 (s, 6H), 0.94 (s, 9H), 3.71 (s, 3H), 4.03 (s, 3H), 4.72 (s, 2H), 5.95 (s, 2H), 6.63 (d, 1H), 6.7 (s, 1H), 6.94 (d, 1H), 6.99 (s, 1H), 7.38 (s, 1H), 8.62 (s, 1H); Mass Spectrum: $M+H^+$ 494. A solution of that material (0.38 g) in THF (6 ml) was treated with tetra-n-butylammonium fluoride (1M solution in THF; 1.5 ml) at ambient temperature for 5 hours. The reaction mixture was partitioned between ethyl acetate and a saturated aqueous ammonium chloride solution. The organic layer was separated, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of hexane and ethyl acetate as eluent. The product so obtained was trituated under diethyl ether. There was thus obtained the required product as a solid (0.197 g); NMR Spectrum: ($DMSOd_6$) 3.92 (d, 6H), 4.48 (d, 2H), 5.2 (t, 1H), 5.98 (s, 2H), 6.83 (d, 1H), 6.95 (d, 1H), 7.3 (s, 1H), 7.78 (s, 1H), 8.41 (s, 1H), 9.48 (s, 1H); Mass Spectrum: $M+H^+$ 380.

The 4-tert-butyldimethylsilyloxymethyl-2,3-methylenedioxyaniline used as a starting material was prepared as follows :-

A mixture of 2,3-dihydroxy-4-nitrobenzaldehyde (J. Med. Chem., 1992, 35, 4584-4588; 7.4 g), bromochloromethane (12.7 ml), caesium carbonate (25.4 g) and DMF (95 ml) was stirred and heated to 110°C for 3 hours. A further portion of bromochloromethane (6.0 ml) was added and the mixture was further heated to 110°C for 3 hours. A third portion of bromochloromethane (3.0 ml) was added and the mixture was further heated to 110°C for 1 hour. The mixture was poured into 2N aqueous hydrochloric acid solution (500 ml) and stirred for 15 minutes. Ethyl acetate (500 ml) was added and the mixture was filtered. The organic layer was washed with a saturated brine solution, dried over magnesium sulphate and evaporated. The crude product was purified by column chromatography on silica using a 1:1 mixture of isohexane and ethyl acetate as eluent. There was thus obtained

2,3-methylenedioxy-4-nitrobenzaldehyde as a yellow solid (5.3 g); NMR Spectrum: ($DMSOd_6$) 6.49 (s, 2H), 7.37 (d, 1H), 7.64 (d, 1H), 10.10 (br s, 1H).

Sodium borohydride (0.75 g) was added portionwise to an ice-cooled mixture of 2,3-methylenedioxy-4-nitrobenzaldehyde (1.3 g) in methanol (35 ml) and the resultant mixture was stirred for 2 hours and allowed to warm to ambient temperature. The mixture was partitioned between ethyl acetate and a 2N aqueous hydrochloric acid solution. The organic layer was dried over magnesium sulphate and evaporated. There was thus obtained 2,3-methylenedioxy-4-nitrobenzyl alcohol as a solid (0.93 g); NMR Spectrum: ($CDCl_3$) 4.67 (d, 2H), 5.43 (t, 1H), 6.18 (s, 2H), 6.96 (d, 1H), 7.57 (d, 1H).

tert-Butyldimethylsilyl chloride (0.462 g) was added to a mixture of 2,3-methylenedioxy-4-nitrobenzyl alcohol (0.55 g), triethylamine (0.47 g), N,N-dimethylaminopyridine (0.01 g) and DMF (5 ml) and the mixture was stirred at ambient temperature for 2 hours. The resultant mixture was evaporated and the residue was partitioned between ethyl acetate and a dilute aqueous citric acid solution. The organic layer was dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of hexane and ethyl acetate as eluent. There was thus obtained tert-butyldimethylsilyl 2,3-methylenedioxy-4-nitrobenzyl ether as a solid (0.68 g); NMR Spectrum: ($CDCl_3$) 0.1 (s, 6H), 0.95 (s, 9H), 4.74 (s, 2H), 6.22 (s, 2H), 7.08 (d, 1H), 7.62 (d, 1H).

The material so obtained was added to a stirred mixture of hydrazine hydrate (0.36 ml). Raney nickel (50% dispersion in water; 0.18 g) and methanol (24 ml) and the reaction mixture was stirred at ambient temperature for 0.5 hours. The mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of hexane and ethyl acetate as eluent. There was thus obtained 4-tert-butyldimethylsilyloxymethyl-2,3-methylenedioxyaniline as an oil (0.56 g); NMR Spectrum: ($CDCl_3$) 0.1 (s, 6H), 0.92 (s, 9H), 3.52 (br s, 2H), 4.62 (s, 2H), 5.92 (s, 2H), 6.31 (d, 1H), 6.73 (d, 1H).

[16] The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 2.18 (s, 3H), 3.93 (2 s, 6H), 5.97 (s, 2H), 6.76 (s, 2H), 7.3 (s, 1H), 7.78 (s, 1H), 8.4 (s, 1H), 9.44 (s, 1H); Mass Spectrum: $M+H^+$ 364.

The 4-methyl-2,3-methylenedioxyaniline used as a starting material was prepared as follows :-

A mixture of 2,3-methylenedioxy-4-nitrobenzyl alcohol (0.35 g), isopropyl isocyanate (2 ml), toluene (2 ml) and acetonitrile (2 ml) was heated to 70°C for 12 hours. The mixture was evaporated and the residue was triturated under hexane. There was thus obtained 2,3-methylenedioxy-4-nitrobenzyl N-isopropylcarbamate as a solid (0.37 g); NMR Spectrum: ($CDCl_3$) 1.18 (d, 6H), 3.83 (m, 1H), 4.6 (br s, 1H), 5.12 (s, 2H), 6.25 (s, 2H), 6.95 (d, 1H), 7.59 (d, 1H).

A mixture of a portion (0.2 g) of the material so obtained, 10% palladium-on-carbon catalyst (0.05 g) and ethyl acetate (5 ml) was stirred under an atmosphere pressure of hydrogen for 12 hours. The mixture was filtered and the filtrate was evaporated. There was thus obtained 4-methyl-2,3-methylenedioxyaniline as an oil (0.089 g); NMR Spectrum: ($CDCl_3$) 2.13 (s, 3H), 3.45 (br s, 2H), 5.91 (s, 2H), 6.23 (d, 1H), 6.51 (d, 1H).

[17] The product gave the following characterising data; NMR Spectrum: ($CDCl_3$) 3.52 (s, 3H), 3.93 (s, 2H), 4.0 (s, 3H), 5.93 (s, 2H), 6.6 (d, 1H), 6.66 (s, 1H), 6.67 (d, 1H), 6.9 (s, 1H), 7.28-7.3 (m, 5H), 7.34 (s, 1H), 8.6 (s, 1H); Mass Spectrum: $M+H^+$ 440.

The 4-benzyl-2,3-methylenedioxyaniline used as a starting material was prepared as follows :-

A mixture of 4-iodo-2,3-methylenedioxyaniline (3.0 g), 1,2-bis(chlorodimethylsilyl)ethane (2.57 g), triethylamine (2.33 g) and methylene dichloride (60 ml) was stirred at ambient temperature for 88 hours. The resultant mixture was evaporated. Isohexane was added to the residue and the mixture was filtered. The filtrate was evaporated and the resultant residue was purified by column chromatography on neutral alumina using isohexane as eluent. There was thus obtained N-(4-iodo-2,3-methylenedioxyphenyl)-2,2,5,5-tetramethyl-1,2,5-azadisilolidine as a solid (2.85 g); NMR Spectrum: ($CDCl_3$) 0.1 (s, 12H), 0.82 (s, 4H), 5.9 (s, 2H), 6.26 (d, 1H), 6.98 (d, 1H).

n-Butyllithium (1.6M in THF, 1.35 ml) was added to a solution of N-(4-iodo-2,3-methylenedioxyphenyl)-2,2,5,5-tetramethyl-1,2,5-azadisilolidine (0.8 g) in THF (12 ml) that had been cooled to -70°C and the mixture was stirred at -70°C for 30 minutes. Benzaldehyde (0.23 g) was added and the mixture was stirred at -70°C for 2 hours and then allowed to warm to 0°C. The resultant mixture was poured into a cooled 1N aqueous hydrochloric acid solution and stirred for 5 minutes and extracted with diethyl ether. The aqueous phase was basified with a 40% aqueous sodium hydroxide solution and extracted with diethyl ether. The organic phase was washed with a saturated brine solution, dried over magnesium sulphate and evaporated. The material so obtained was purified by column

chromatography on silica using a 1:4 mixture of isohexane and tert-butyl methyl ether as eluent. There was thus obtained 4-(α-hydroxybenzyl)-2,3-methylenedioxyaniline as an oil (0.213 g); NMR Spectrum: ($CDCl_3$) 2.4 (s, 1H), 3.54 (br s, 2H), 5.9 (s, 1H), 5.92 (s, 2H), 6.26 (d, 1H), 6.6 (d, 1H), 7.25 (m, 1H), 7.32 (t, 2H), 7.4 (d, 2H).

A mixture of the material so obtained, 10% palladium-on-carbon catalyst (0.02 g) and ethanol (10 ml) was stirred at ambient temperature under an atmosphere pressure of hydrogen for 12 hours. The mixture was filtered and the residue was evaporated. There was thus obtained 4-benzyl-2,3-methylenedioxyaniline as a colourless oil (0.137 g); Mass Spectrum: $M+H^+$ 228.

[18] The product gave the following characterising data; NMR Spectrum: ($CDCl_3$) 2.48 (s, 3H), 3.75 (s, 3H), 4.03 (s, 3H), 6.0 (s, 2H), 6.61 (d, 1H), 6.66 (br s, 1H), 6.82 (d, 1H), 6.98 (s, 1H), 7.38 (s, 1H), 8.62 (s, 1H); Mass Spectrum: $M+H^+$ 396.

The 4-methylthio-2,3-methylenedioxyaniline used as a starting material was prepared as follows :-

n-Butyllithium (1.6M in hexane, 1.28 ml) was added during 10 minutes to a solution of N-(4-iodo-2,3-methylenedioxyphenyl)-2,2,5,5-tetramethyl-1,2,5-azadisilolidine (0.75 g) in THF (25 ml) that had been cooled to -78°C and the mixture was stirred at -78°C for 25 minutes. Dimethyl disulphide (0.288 g) was added and the mixture was stirred at –78°C for 3 hours. The resultant mixture was allowed to warm to 0°C. A 1N aqueous hydrochloric acid solution (25 ml) was added and the mixture was stirred for 10 minutes. The mixture was washed with diethyl ether. The aqueous phase was basified to pH11 by the addition of a concentrated aqueous sodium hydroxide solution and extracted with methylene chloride. The organic extract was washed with a saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated. The material so obtained was purified by column chromatography on reverse-phase silica using a decreasingly polar gradient of acetonitrile in water (plus 0.1% trifluoroacetic acid) as eluent. There was thus obtained 4-methylthio-2,3-methylenedioxyaniline as an oil which crystallized on standing (0.13 g); NMR Spectrum: ($CDCl_3$) 2.38 (s, 3H), 3.59 (br s, 2H), 5.98 (s, 2H), 6.27 (d, 1H), 6.74 (d, 1H).

[19] The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 1.96 (m, 2H), 2.18 (s, 3H), 2.25-2.5 (m, 10H), 3.94 (s, 3H), 4.22 (t, 2H), 6.11 (s, 2H), 6.76 (d, 1H), 7.22 (d, 1H), 7.35 (s, 1H), 7.75 (s, 1H), 8.48 (s, 1H), 9.54 (s, 1H); Mass Spectrum: $M-H^-$ 600.

The 4-chloro-3-cyano-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline used as a starting material was prepared as follows :-

A solution of diisopropyl azodicarboxylate (12.1 ml) in methylenechloride (50 ml) was added dropwise during 30 minutes to a stirred mixture of 4-chloro-3-cyano-7-hydroxy-6-methoxyquinoline (12 g), 1-(3-hydroxypropyl)-4-methylpiperazine (9.7 g), triphenylphosphine (16.1 g) and methylenedichloride (200 ml) that had been cooled to 5°C. The resultant mixture was allowed to warm to ambient temperature and was then stirred for 1 hour. Further portions of diisopropyl azodicarboxylate (1.2 ml) and triphenylphosphine (1.6 g) were added and the mixture was stirred at ambient temperature for a further 1 hour. The mixture was poured into water and the organic layer was separated, washed with a saturated brine solution, dried over magnesium sulphate and evaporated. The material so obtained was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained the required starting material as a solid (14.5 g); NMR Spectrum: ($DMSOd_6$) 1.95 (m, 2H), 2.13 (s, 3H), 2.24-2.5 (m, 10H), 4.0 (s, 3H), 4.25 (t, 2H), 7.43 (s, 1H), 7.51 (s, 1H), 8.95 (s, 1H); Mass Spectrum: $M+H^+$ 375 and 377.

[20] The product gave the following characterising data; NMR Spectrum: ($CDCl_3$) 2.88 (m, 2H), 3.37 (s, 3H), 3.62 (t, 2H), 3.72 (s, 3H), 4.03 (s, 3H), 5.93 (s, 2H), 6.64 (d, 1H), 6.68 (s, 1H), 6.76 (d, 1H), 6.95 (s, 1H), 7.37 (s, 1H), 8.61 (s, 1H); Mass Spectrum: $M+H^+$ 408.

The 4-(2-methoxyethyl)-2,3-methylenedioxyaniline used as a starting material was prepared as follows :-

Potassium tert-butoxide (1M solution in THF; 1.35 ml) was added to a mixture of methoxymethyltriphenylphosphonium chloride (0.42 g) and THF (3 ml) and the resultant mixture was stirred at ambient temperature for 0.5 hours. A solution of 2,3-methylenedioxy-4-nitrobenzaldehyde (0.12 g) in THF (2 ml) was added and the reaction mixture was stirred at ambient temperature for 1 hour. The mixture was diluted with a saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The organic phase was dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and ethyl acetate as eluent. There was thus obtained 4-(2-methoxyethenyl)-2,3-methylenedioxy-1-nitrobenzene as a solid (0.108 g) in the form of a 2.7:1 mixture of Z and E isomers; NMR Spectrum: ($CDCl_3$) 3.77 (s, 3H), 5.72 (d, 1H), 6.24 (s, 2H), 6.74 (d, 1H), 7.48 (d, 1H), 7.56 (d, 1H).

A mixture of the material so obtained, 10% palladium-on-carbon (0.02 g) and ethyl acetate (4 ml) was stirred under an atmosphere pressure of hydrogen at ambient temperature for 12 hours. The mixture was filtered and the filtrate was evaporated. The residue was

purified by column chromatography on silica using increasingly polar mixtures of hexane and ethyl acetate as eluent. There was thus obtained 4-(2-methoxyethyl)-2,3-methylenedioxyaniline as an oil (0.05 g); NMR Spectrum: ($CDCl_3$) 2.78 (t, 2H), 3.36 (s, 3H), 3.48 (br s, 2H), 3.57 (t, 2H), 5.92 (s, 2H), 6.27 (d, 1H), 6.54 (d, 1H).

[21] The product gave the following characterising data; NMR Spectrum: ($CDCl_3$) 2.49 (t, 4H), 3.5 (s, 2H), 3.71 (t, 4H), 3.76 (s, 3H), 4.03 (s, 3H), 5.94 (s, 2H), 6.64 (d, 1H), 6.74 (s, 1H), 6.86 (d, 1H), 7.02 (s, 1H), 7.37 (s, 1H), 8.61 (s, 1H); Mass Spectrum: $M-H^-$ 447.

The 2,3-methylenedioxy-4-morpholinomethylaniline used as a starting material was prepared as follows :-

Sodium triacetoxyborohydride (1.06 g) was added to a stirred mixture of 2,3-methylenedioxy-4-nitrobenzaldehyde (0.7 g), morpholine (0.34 g), acetic acid (0.23 ml) and THF (20 ml) and the resultant mixture was stirred at ambient temperature for 3 hours. The mixture was partitioned between ethyl acetate and a saturated aqueous sodium bicarbonate solution. The organic phase was dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and a saturated methanolic ammonia solution as eluent. There was thus obtained 2,3-methylenedioxy-4-morpholinomethyl-1-nitrobenzene as a solid (0.62 g); NMR Spectrum: ($CDCl_3$) 2.5 (t, 4H), 3.66 (s, 2H), 3.72 (t, 4H), 6.22 (s, 2H), 7.02 (d, 1H), 7.59 (d, 1H).

2,3-Methylenedioxy-4-morpholinomethyl-1-nitrobenzene (0.1 g) was added to a stirred mixture of Raney nickel (50% in water, 0.03 g), hydrazine hydrate (0.074 g) and methanol (4 ml) and the mixture was stirred at ambient temperature for 1.5 hours. The mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and ethyl acetate as eluent. There was thus obtained 2,3-methylenedioxy-4-morpholinomethylaniline (0.085 g); NMR Spectrum: ($CDCl_3$) 2.49 (t, 4H), 3.43 (s, 2H), 3.71 (t, 4H), 5.95 (s, 2H), 6.28 (d, 1H), 6.66 (d, 1H).

[22] The product gave the following characterising data; NMR Spectrum: ($CDCl_3$) 2.26 (s, 6H), 3.46 (s, 2H), 3.74 (s, 3H), 4.04 (s, 3H), 5.97 (s, 2H), 6.63 (d, 1H), 6.68 (s, 1H), 6.82 (d, 1H), 7.01 (s, 1H), 7.37 (s, 1H), 8.62 (s,1H); Mass Spectrum: $M-H^-$ 405.

The 4-dimethylaminomethyl-2,3-methylenedioxyaniline used as a starting material was prepared from 2,3-methylenedioxy-4-nitrobenzaldehyde and dimethylamine using analogous procedures to those decribed in Note [21] immediately above. The required starting material

gave the following characterising data; NMR Spectrum: ($CDCl_3$) 2.24 (s, 6H), 3.35 (s, 2H), 3.51 (br s, 2H), 5.95 (s, 2H), 6.28 (d, 1H), 6.60 (d, 1H).

[23] The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 3.98 (s, 6H), 6.17 (s, 2H), 6.97 (d, 1H), 7.27 (d, 1H), 7.35 (s, 1H), 7.46 (s, 1H), 7.78 (s, 1H), 8.5 (d, 2H), 9.64 (s, 1H); Mass Spectrum: $M+H^+$ 417.

The 2,3-methylenedioxy-4-oxazol-5-ylaniline used as a starting material was prepared as follows :-

A mixture of 2,3-methylenedioxy-4-nitrobenzaldehyde (0.1 g), tosylmethyl isocyanide (0.109 g), potassium carbonate (0.078 g) and methanol (5 ml) was stirred and heated to 50°C for 1 hour. The mixture was partitioned between methylene chloride and water. The organic phase was dried over magnesium sulphate and evaporated. There was thus obtained 2,3-methylenedioxy-4-oxazol-5-yl-1-nitrobenzene as a solid (0.13 g); NMR Spectrum: ($DMSOd_6$) 6.48 (s, 2H), 7.35 (d, 1H), 7.7 (m, 2H), 8.63 (s, 1H).

A mixture of the material so obtained, 10 % palladium-on-carbon (0.03 g), methanol (1 ml) and ethyl acetate (3 ml) was stirred at ambient temperature under an atmosphere pressure of hydrogen for 12 hours. The mixture was filtered and the filtrate was evaporated. There was thus obtained 2,3-methylenedioxy-4-oxazol-5-ylaniline as a solid (0.048 g); NMR Spectrum: ($CDCl_3$) 5.18 (s, 2H), 6.08 (s, 2H), 6.35 (d, 1H), 6.93 (d, 1H), 7.14 (s, 1H), 8.28 (s, 1H).

[24] The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 1.96 (m, 2H), 2.15 (s, 3H), 2.4-2.72 (m, 10H), 2.79 (t, 2H), 3.22 (s, 3H), 3.51 (t, 2H), 3.91 (s, 3H), 4.19 (t, 2H), 5.98 (s, 2H), 6.79 (m, 2H), 7.3 (s, 1H), 7.74 (s, 1H), 8.4 (s, 1H), 9.45 (s, 1H); Mass Spectrum: $M-H^-$ 532.

[25] The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 1.98 (m, 2H), 2.68 (t, 2H), 2.83 (t, 2H), 2.93 (br s, 4H), 3.1 (br s, 4H), 3.28 (s, 3H), 3.57 (t, 2H), 3.96 (s, 3H), 4.03 (t, 2H), 5.99 (s, 2H), 6.81 (m, 2H), 7.36 (s, 1H), 7.78 (s, 1H), 8.43 (s, 1H), 9.45 (s, 1H); Mass Spectrum: $M+H^+$ 569.

The 4-chloro-3-cyano-7-[3-(1,1-dioxotetrahydro-4H-thiazin-4-yl)propoxy]-6-methoxyquinoline used as a starting material was prepared as follows :-

A mixture of 3-aminopropan-1-ol (0.65 ml) and divinyl sulphone (1 g) was heated to 110°C for 45 minutes. The mixture was allowed to cool to ambient temperature and was purified by column chromatography on silica using a 19:1 mixture of methylene chloride and methanol as eluent. There was thus obtained 4-(3-hydroxypropyl)-1,1-dioxotetrahydro-

4H-thiazine (0.8 g); NMR Spectrum: ($CDCl_3$) 1.7-1.8 (m, 2H), 2.73 (t, 2H), 3.06 (br s, 8H), 3.25 (s, 1H), 3.78 (t, 2H); Mass Spectrum: $M+H^+$ 194.

Diethyl azodicarboxylate (1.72 g) was added dropwise to a suspension of 4-chloro-3-cyano-7-hydroxy-6-methoxyquinoline (1 g), 4-(3-hydroxypropyl)-1,1-dioxotetrahydro-4H-thiazine (1.23 g), triphenyl phosphine (1.45 g) and methylene chloride (10 ml) and the mixture was stirred at ambient temperature for 16 hours. The resultant mixture was washed with water and with a saturated brine solution. The organic phase was dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride, ethyl acetate and a saturated methanolic ammonia solution as eluent. The material so obtained was triturated under diethyl ether. There was thus obtained 4-chloro-3-cyano-7-[3-(1,1-dioxotetrahydro-4H-thiazin-4-yl)propoxy]-6-methoxyquinoline (0.15 g); NMR Spectrum: ($DMSOd_6$) 1.96 (m, 2H), 2.64 (t, 2H), 2.88–2.93 (m, 4H), 3.07–3.12 (m, 4H), 4.0 (s, 3H), 4.29 (t, 2H), 7.44 (s, 1H), 7.55 (s, 1H), 8.96 (s, 1H); Mass Spectrum: $M+H^+$ 410.

[26] The product gave the following characterising data; NMR Spectrum: ($DMSOd_6$) 2.25 (m, 2H), 2.78 (t, 2H), 3.25 (s, 3H), 3.54 (t, 2H), 3.81 (t, 2H), 3.93 (s, 3H), 4.28 (t, 2H), 5.97 (s, 2H), 6.78 (m, 2H), 7.33 (s, 1H), 7.77 (s, 1H), 8.39 (s, 1H), 9.42 (s, 1H); Mass Spectrum: $M+H^+$ 470.

[27] The product gave the following characterising data; NMR Spectrum: ($CDCl_3$) 2.25 (s, 3H), 3.74 (s, 3H), 4.02 (s, 3H), 5.9 (s, 2H), 6.45 (d, 1H), 6.56 (d, 1H), 6.78 (br s, 1H), 7.02 (s, 1H), 7.36 (s, 1H), 8.6 (s, 1H); Mass Spectrum: $M+H^+$ 364.

The 5-methyl-2,3-methylenedioxyaniline used as a starting material was prepared as follows :-

n-Butyllithium (1.6M in hexane; 1.1 ml) was added dropwise to a solution of N-(5-bromo-2,3-methylenedioxyphenyl)-2,2,5,5-tetramethyl-1,2,5-azadisilolidine (0.6 g) in THF (12 ml) that had been cooled to -70°C and the mixture was stirred at -70°C for 1hour. Methyl iodide (0.285 g) was added and the mixture was stirred and allowed to warm to 0°C during 2 hours. A 1N aqueous hydrochloric acid solution was added and the resultant mixture was stirred at 0°C for 5 minutes. The mixture was washed with diethyl ether. The aqueous phase was basified by the addition of 40% aqueous sodium hydroxide solution and extracted with diethyl ether. The organic phase was washed with a saturated brine solution, dried over magnesium sulphate and evaporated. The material so obtained was purified by column chromatography on reversed-phase silica using decreasingly polar mixtures of acetonitrile and

a 1% solution of trifluoroacetic acid in water as eluent. There was thus obtained 5-methyl-2,3-methylenedioxyaniline (0.086 g) as a colourless oil; NMR Spectrum: ($CDCl_3$) 2.2 (s, 3H), 3.08 (br s, 2H), 5.87 (s, 2H), 6.13 (d, 1H), 6.18 (d, 1H).

[28] The product gave the following characterising data; NMR Spectrum: ($CDCl_3$) 3.32 (s, 3H), 3.77 (s, 3H), 4.03 (s, 3H), 4.32 (s, 2H), 5.96 (s, 2H), 6.63 (d, 1H), 6.72 (d, 1H), 6.77 (s, 1H), 7.02 (s, 1H), 7.37 (s, 1H), 8.61 (s, 1H); Mass Spectrum: $M+H^+$ 394.

The 5-methoxymethyl-2,3-methylenedioxyaniline used as a starting material was prepared as follows :-

n-Butyllithium (1.6M in hexane; 1.1 ml) was added dropwise to a solution of N-(5-bromo-2,3-methylenedioxyphenyl)-2,2,5,5-tetramethyl-1,2,5-azadisilolidine (0.6 g) in THF (12 ml) that had been cooled to -70°C and the mixture was stirred at -70°C for 1hour. Bromomethyl methyl ether (0.314 g) was added and the mixture was stirred and allowed to warm to 0°C during 2 hours. A 1N aqueous hydrochloric acid solution was added and the resultant mixture was stirred at 0°C for 5 minutes. The mixture was washed with diethyl ether. The aqueous phase was basified by the addition of 40% aqueous sodium hydroxide solution and extracted with diethyl ether. The organic phase was washed with a saturated brine solution, dried over magnesium sulphate and evaporated. The material so obtained was purified by column chromatography on silica using a 4:1 mixture of tert-butyl methyl ether and isohexane as eluent. Thus was obtained 5-methoxymethyl-2,3-methylenedioxyaniline (0.163 g) as a colourless oil; NMR Spectrum: ($CDCl_3$) 3.34 (s, 3H), 3.58 (br s, 2H), 4.29 (s, 2H), 5.91 (s, 2H), 6.31 (d, 1H), 6.34 (d, 1H).

Example 11

3-cyano-7-[(2R)-2-hydroxy-3-morpholinopropoxy]-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline

A mixture of 3-cyano-7-[(2R)-2,3-epoxypropoxy]-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline (0.1 g), morpholine (0.11 g) and propanol (5 ml) was stirred and heated to 80°C for 3 hours. The resultant mixture was evaporated and the residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. The material so obtained was triturated under diethyl ether to give the title compound (0.04 g); NMR Spectrum: ($DMSOd_6$) 2.35-2.52 (m, 6H), 3.56 (m, 4H), 3.93 (s, 3H), 4.0-4.1 (m, 2H), 4.17 (m, 1H), 4.9 (d, 1H), 5.98 (s, 2H), 6.9-

6.92 (m, 3H), 7.33 (s, 1H), 7.86 (s, 1H), 8.4 (s, 1H), 9.48 (br s, 1H); Mass Spectrum: $M-H^-$ 477.

The 3-cyano-7-[(2R)-2,3-epoxypropoxy]-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline used as a starting material was prepared as follows :-

(2R)-(-)-Glycidyl tosylate (0.52 g) was added to a mixture of 3-cyano-7-hydroxy-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline (0.67 g), potassium carbonate (0.87 g) and DMA (15 ml) and the mixture was stirred and heated to 60°C for 3 hours. The resultant mixture was evaporated and the residue was partitioned between methylene chloride and water. The organic phase was washed with water and with a saturated brine solution, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained 3-cyano-7-[(2R)-2,3-epoxypropoxy]-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline as a solid (0.3 g); NMR Spectrum: ($DMSOd_6$) 2.75 (m, 1H), 2.88 (m, 1H), 3.4 (m, 1H), 3.95 (s, 3H), 3.95-4.01 (m, 1H), 4.53 (m, 1H), 5.98 (s, 2H), 6.8-6.92 (m, 3H), 7.33 (s, 1H), 7.79 (s, 1H), 8.41 (s, 1H), 9.51 (s, 1H); Mass Spectrum: $M+H^+$ 392.

Example 12

7-[(2R)-3-(4-acetylpiperazin-1-yl)-2-hydroxypropoxy]-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline

Using an analogous procedure to that described in Example 11, 3-cyano-7-[(2R)-2,3-epoxypropoxy]-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline was reacted with 1-acetylpiperazine to give the title compound in 35% yield; NMR Spectrum: ($DMSOd_6$) 1.96 (s, 3H), 2.34-2.54 (m, 6H), 3.35-3.45 (m, 4H), 3.94 (s, 3H), 4.0-4.1 (m, 2H), 4.13-4.21 (m, 1H), 4.94 (d, 1H), 5.97 (s, 2H), 6.80-6.92 (m, 3H), 7.23 (s, 1H), 7.76 (s, 1H), 8.4 (s, 1H), 9.49 (s, 1H); Mass Spectrum: $M+H^+$ 520.

Example 13

3-cyano-7-[(2R)-2-hydroxy-3-methoxypropoxy]-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline

A mixture of 3-cyano-7-[(2R)-2,3-epoxypropoxy]-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline (0.1 g), a methanolic sodium methoxide solution

(25%, 1 ml) and methanol (5 ml) was stirred at ambient temperature for 18 hours. The mixture was evaporated and the residue was dissolved in methylene chloride and washed with water and with a saturated brine solution and dried over magnesium sulphate. The organic phase was evaporated and the residue was was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. The resultant gum was triturated under diethyl ether to give the title compound as a solid (0.035 g); NMR Spectrum: ($DMSOd_6$) 3.29 (s, 3H), 3.32-3.49 (m, 2H), 3.94 (s, 3H), 3.98-4.17 (m, 3H), 5.15 (m, 1H), 5.98 (s, 2H), 6.89-6.92 (m, 3H), 7.3 (s, 1H), 7.78 (s, 1H), 8.4 (s, 1H), 9.48 (br s, 1H); Mass Spectrum: $M+H^+$ 424.

Example 14

3-cyano-6-methoxy-4-(2,3-methylenedioxyphenoxy)-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline

Potassium carbonate (0.055 g) was added to a solution of 2,3-methylenedioxyphenol (0.041 g) in DMF (3 ml) and the mixture was stirred at ambient temperature for 10 minutes. 4-Chloro-3-cyano-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline (0.1 g) was added and the mixture was stirred and heated to 95°C for 2 hours. The resultant mixture was cooled to ambient temperature and filtered. The filtrate was evaporated and the residue was purified by colum chromatography on silica using initially increasingly polar mixtures of methylene chloride and methanol followed by increasingly polar mixtures of methylene chloride and a saturated methanolic ammonia solution as eluent. There was thus obtained the title compound as a solid (0.069 g); NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.3-2.4 (m, 2H), 3.0 (s, 3H), 3.2-4.0 (m, 8H), 3.5 (m, 2H), 3.95 (s, 3H), 4.4 (m, 2H), 6.05 (s, 2H), 6.8 (m, 1H), 6.9 (m, 2H), 7.6 (s, 1H), 7.62 (s, 1H), 9.1 (s, 1H); Mass Spectrum: $M+H^+$ 477.

The 4-chloro-3-cyano-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline used as a starting material was prepared as follows :-

A mixture of 3-bromopropanol (20 ml), N-methylpiperazine (29 ml), potassium carbonate (83 g) and ethanol (200 ml) was stirred and heated to reflux for 20 hours. The mixture was cooled to ambient temperature and filtered. The filtrate was evaporated and the residue was triturated under diethyl ether. The resultant mixture was filtered and the filtrate was evaporated. The residue was purified by distillation at about 60-70°C under about 0.2 mm Hg to give 1-(3-hydroxypropyl)-4-methylpiperazine (17 g); NMR Spectrum: ($CDCl_3$) 1.72 (m, 2H), 2.3 (s, 3H), 2.2-2.8 (m, 8H), 2.6 (t, 2H), 3.8 (t, 2H), 5.3 (br s, 1H).

Diethyl azodicarboxylate (0.25 g) was added dropwise to a suspension of 4-chloro-3-cyano-7-hydroxy-6-methoxyquinoline (0.2 g), 1-(3-hydroxypropyl)-4-methylpiperazine (0.202 g), triphenyl phosphine (0.447 g) and methylene chloride (5 ml) and the mixture was stirred at ambient temperature for 2 hours. The resultant mixture was evaporated and the residue was purified by column chromatography on silica using initially increasingly polar mixtures of methylene chloride and ethyl acetate followed by increasingly polar mixtures of methylene chloride, ethyl acetate and a saturated methanolic ammonia solution as eluent. The material so obtained was triturated under diethyl ether. The resultant solid was isolated and dried under vacuum to give the required starting material (0.15 g); NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 1.95-2.05 (m, 2H), 2.2 (s, 3H), 2.25-2.5 (m, 10H), 4.05 (s, 3H), 4.3 (m, 2H), 7.45 (s, 1H), 7.58 (s, 1H), 9.0 (s, 1H); Mass Spectrum: $M+H^+$ 375 and 377.

The 2,3-methylenedioxyphenol used as a starting material was prepared as follows :-

3-Chloroperbenzoic acid (70% pure; 10.3 g) was added to a solution of 2,3-methylenedioxybenzaldehyde (3 g) in chloroform and the mixture was heated to reflux for 1 hour. The organic phase was washed in turn with a saturated aqueous sodium bicarbonate solution, water and a saturated brine solution, dried over magnesium sulphate and evaporated. A mixture of the material so obtained, 6N aqueous hydrochloric acid (90 ml) and methanol (90 ml) was stirred and heated to 80°C for 30 minutes. The mixture was cooled to ambient temperature and concentrated by evaporation of the bulk of the solvent. The residue was partitioned between methylene chloride and a saturated aqueous sodium bicarbonate solution. The organic phase was washed with water and with a saturated brine solution, dried over magnesium sulphate and evaporated. The crude product so obtained was purified by column chromatography on silica using a 9:1 mixture of petroleum ether (b.p 40-60°C) and ethyl acetate as eluent. There was thus obtained 2,3-methylenedioxyphenol as a solid (1.7 g); NMR Spectrum: ($CDCl_3$) 4.85 (br s, 1H), 5.95 (s, 2H), 6.45 (d, 1H), 6.5 (d, 1H), 6.75 (t, 1H).

Example 15

4-(6-bromo-2,3-methylenedioxyphenoxy)-3-cyano-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline

Using an analogous procedure to that described in Example 14, 4-chloro-3-cyano-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline was reacted with 6-bromo-2,3-methylenedioxyphenol to give the title compound as a solid in 52% yield; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.25-2.4 (m, 2H), 2.95 (s, 3H), 3.2-4.0 (m, 8H), 3.48 (m,

2H), 3.98 (s, 3H), 4.35 (m, 2H), 6.02 (s, 1H), 6.08 (s, 1H), 6.92 (d, 1H), 7.25 (d, 1H), 7.6 (d, 2H), 8.9 (s, 1H); Mass Spectrum: $M+H^+$ 555 and 557.

The 6-bromo-2,3-methylenedioxyphenol used as a starting material was prepared as follows :-

A solution of bromine (0.074 ml) in chloroform (2 ml) was added dropwise to a stirred mixture of 2,3-methylenedioxyphenol (0.2 g), silver trifluoroacetate (0.32 g) and chloroform (3 ml) and the resultant mixture was stirred at ambient temperature for 2 hours. The mixture was filtered and the filtrate was adsorbed onto silica and purified by column chromatography on silica using a 9:1 mixture of petroleum ether (b.p. 40-60°C) and ethyl acetate as eluent. There was thus obtained the desired material (0.217 g) as a solid; NMR Spectrum: ($CDCl_3$) 5.35 (s, 1H), 6.05 (s, 2H), 6.4 (d, 1H), 6.95 (d, 1H); Mass Spectrum: $[M-H]^-$ 215 and 217.

Example 16

3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-piperazin-1-ylpropoxy)quinoline

A mixture of 7-[3-(4-tert-butoxycarbonylpiperazin-1-yl)propoxy]-3-cyano-6-methoxy-4-(2,3-methylenedioxyanilino)quinoline (0.2 g) and trifluoroacetic acid (2 ml) was stirred at ambient temperature for 40 minutes. The mixture was evaporated and the residue was partitioned between methylene chloride and a saturated aqueous sodium bicarbonate solution. The organic layer was dried over magnesium sulphate and evaporated. The residue was triturated under a 1:1 mixture of diethyl ether and isohexane. There was thus obtained the title compound as a solid (0.076 g); NMR Spectrum: ($DMSOd_6$) 1.93 (m, 2H), 2.4–2.64 (m, 6H), 3.1 (s, 4H), 3.95 (s, 3H), 4.22 (t, 2H), 5.98 (s, 2H), 6.8-6.95 (m, 3H), 7.33 (s, 1H), 7.79 (s, 1H), 8.43 (s, 1H), 8.53 (br s, 1H), 9.54 (s, 1H); Mass Spectrum: $M-H^-$ 460.

Example 17

3-cyano-4-(6-cyano-2,3-methylenedioxyanilino)-6,7-dimethoxyquinoline

Tris(dibenzylideneacetone)dipalladium (0.039 g) was added to a mixture of a 4:1 mixture (0.25 g) of 3-cyano-4-(6-iodo-2,3-methylenedioxyanilino)-6,7-dimethoxyquinoline and 3-cyano-4-(4,6-diiodo-2,3-methylenedioxyanilino)-6,7-dimethoxyquinoline (Example 10, Note [11]), zinc cyanide (0.092 g), diphenylphosphinoferrocene (0.046 g), zinc powder (0.017 g) and DMA (15 ml) and the resultant mixture was stirred and heated to 110°C for 1 hour. The mixture was cooled to ambient temperature and partitioned between ethyl acetate and water. The organic layer was

dried over magnesium sulphate and evaporated and the residue was purified by column chromatography on silica using increasingly polar mixtures of hexane and ethyl acetate as eluent. There were thus obtained in turn :-

3-cyano-4-(6-cyano-2,3-methylenedioxyanilino)-6,7-dimethoxyquinoline as a solid (0.082 g); NMR Spectrum: ($DMSOd_6$) 3.96 (s, 3H), 3.98 (s, 3H), 6.17 (s, 2H), 7.01 (s, 1H), 7.4 (s, 1H), 7.47 (d , 1H), 7.88 (s, 1H), 8.45 (s, 1H), 9.5 (br s, 1H); Mass Spectrum: $M+H^+$ 375; and

3-cyano-4-(4,6-dicyano-2,3-methylenedioxyanilino)-6,7-dimethoxyquinoline as a solid (0.012 g); NMR Spectrum: (DMSOd6) 3.89 (s, 3H), 3.98 (s, 3H), 6.24 (s, 2H), 7.21 (s, 1H), 7.8 (s, 2H), 8.45 (s, 1H), 11.7 (br s, 1H); Mass Spectrum: $M+H^+$ 400.

Example 18

3-cyano-4-(4-cyano-2,3-methylenedioxyanilino)-6,7-dimethoxyquinoline

Tris(dibenzylideneacetone)dipalladium (0.0073 g) was added to a mixture of 3-cyano-4-(4-iodo-2,3-methylenedioxyanilino)-6,7-dimethoxyquinoline (0.05 g), zinc cyanide (0.015 g), diphenylphosphinoferrocene (0.009 g), zinc powder (0.0035 g) and DMA (2 ml) and the resultant mixture was stirred and heated to 110°C for 1 hour. The mixture was cooled to ambient temperature and partitioned between ethyl acetate and water. The organic layer was dried over magnesium sulphate and evaporated and the residue was purified by column chromatography on silica using increasingly polar mixtures of hexane and ethyl acetate as eluent. The material so obtained was triturated under diethyl ether. There was thus obtained 3-cyano-4-(4-cyano-2,3-methylenedioxyanilino)-6,7-dimethoxyquinoline as a solid (0.014 g); NMR Spectrum: ($CDCl_3$) 3.84 (s, 3H), 4.07 (s, 3H), 6.16 (s, 2H), 6.28 (d, 1H), 6.75 (s, 1H), 6.99 (m, 2H), 7.46 (s, 1H), 8.73 (s, 1H); Mass Spectrum: $M+H^+$ 375.

Example 19

4-(6-chloro-4-cyano-2,3-methylenedioxyanilino)-3-cyano-6,7-dimethoxyquinoline

Tris(dibenzylideneacetone)dipalladium (0.039 g) was added to a mixture of 4-(6-chloro-4-iodo-2,3-methylenedioxyanilino)-3-cyano-6,7-dimethoxyquinoline (0.268 g), zinc cyanide (0.086 g), diphenylphosphinoferrocene (0.046 g), zinc powder (0.017 g) and DMA (15 ml) and the resultant mixture was stirred and heated to 110°C for 1 hour. The mixture was cooled to ambient temperature and partitioned between ethyl acetate and water. The organic layer was dried over magnesium sulphate and evaporated and the residue was purified by column chromatography on silica using increasingly polar mixtures of hexane and

ethyl acetate as eluent. The material so obtained was triturated under diethyl ether. There was thus obtained 3-cyano-4-(4-cyano-2,3-methylenedioxyanilino)-6,7-dimethoxyquinoline as a solid (0.11 g); NMR Spectrum: ($DMSOd_6$) 3.94 (s, 3H), 3.98 (s, 3H), 6.21 (s, 2H), 7.28 (s, 1H), 7.4 (s, 1H), 7.79 (s, 1H), 8.36 (s, 1H); Mass Spectrum: $M+H^+$ 409 and 411.

Example 20

3-cyano-4-(4-cyano-2,3-methylenedioxyanilino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline

Using an analogous procedure to that described in Example 19, 3-cyano-4-(4-iodo-2,3-methylenedioxyanilino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline (0.316 g) was reacted with zinc cyanide (0.086 g) to give the title compound as a solid (0.014 g); NMR Spectrum: ($DMSOd_6$) 1.96 (m, 2H), 2.18 (s, 3H), 2.25-2.5 (m, 10H), 3.94 (s, 3H), 4.18 (t, 2H), 6.16 (s, 2H), 6.94 (d, 1H), 7.3 (d, 1H), 7.37 (s, 1H), 7.72 (s, 1H), 8.61 (s, 1H), 9.87 (br s, 1H); Mass Spectrum: $M-H^-$ 499.

Example 21

3-cyano-4-(4-ethynyl-2,3-methylenedioxyanilino)-6,7-dimethoxyquinoline

A mixture of 3-cyano-4-(4-iodo-2,3-methylenedioxyanilino)-6,7-dimethoxyquinoline (0.2 g), trimethylsilylacetylene (0.11 ml), tetrakis(triphenylphosphine)palladium(0) (0.05 g), cuprous iodide (0.01 g) and N,N-diethylamine (4 ml) was stirred and heated to 60°C for 4 hours. The reaction mixture was evaporated and the residue was partitioned between methylene chloride and a 2N aqueous hydrochloric acid solution. The precipitate that was formed was isolated by filtration, washed with methylene chloride and dried. There was thus obtained 3-cyano-6,7-dimethoxy-4-(2,3-methylenedioxy-4-trimethylsilylethynylanilino)quinoline as a solid (0.08 g); Mass Spectrum: $M+H^+$ 446.

A mixture of the material so obtained, potassium carbonate (0.07 g), water (1 ml) and methanol (5 ml) was stirred at ambient temperature for 2 hours. The reaction mixture was evaporated and the residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and ethyl acetate as eluent. The material so obtained was dissolved in a mixture of methylene chloride and diethyl ether and a 1M solution of hydrogen chloride in diethyl ether was added. The resultant solid was isolated, washed with diethyl ether and dried. There was thus obtained the title compound as a hydrochloride

salt (0.055 g); NMR Spectrum: ($DMSOd_6$) 3.99 (s, 3H), 4.0 (s, 3H), 4.46 (s, 1H), 6.22 (s, 2H), 6.97 (d, 1H), 7.04 (d, 1H), 7.47 (s, 1H), 8.15 (s, 1H), 8.97 (s, 1H); Mass Spectrum: $M+H^+$ 374.

Example 22

3-cyano-6-methoxy-4-(2,3-methylenedioxy-4-phenylanilino)-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline

A mixture of 3-cyano-4-(4-iodo-2,3-methylenedioxyanilino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline (0.15 g), phenylboronic acid (0.046 g), tetrakis(triphenylphosphine)palladium(0) (0.01 g), a saturated aqueous sodium bicarbonate solution (2 ml) and 1,2-dimethoxyethane (18 ml) was stirred and heated to 80°C for 5 hours. The reaction mixture was cooled to ambient temperature and partitioned between ethyl acetate and water. The organic layer was dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. The material so obtained was triturated under diethyl ether. There was thus obtained the title compound as a solid (0.085 g); NMR Spectrum: ($DMSOd_6$) 1.95 (m, 2H), 2.17 (s, 3H), 2.24–2.59 (m, 10H), 3.96 (s, 3H), 4.17 (t, 2H), 6.06 (s, 2H), 6.94 (d, 1H), 7.23 (d, 1H), 7.3 (s, 1H), 7.37 (t, 1H), 7.46 (t, 2H), 7.76 (d, 2H), 7.77 (s, 1H), 8.43 (s, 1H), 9.55 (s, 1H); Mass Spectrum: $M-H^-$ 550.

Example 23

3-cyano-6,7-dimethoxy-4-(2,3-methylenedioxy-4-methylsulphonylanilino)quinoline

3-Chloroperoxybenzoic acid (70% technical grade; 0.05 g) was added in one portion to a stirred solution of 3-cyano-6,7-dimethoxy-4-(2,3-methylenedioxy-4-methylthioanilino)quinoline (0.04 g) in chloroform (5 ml) and the mixture was stirred at ambient temperature for 18 hours. The reaction mixture was evaporated to dryness under reduced pressure whilst being cooled to 0°C. The material so obtained was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained the title compound as a solid (0.016 g); NMR Spectrum: ($DMSOd_6$) 3.13 (s, 3H), 3.82 (s, 3H), 3.88 (s, 3H), 6.05 (s, 2H), 6.62 (d, 1H), 7.03 (d, 1H), 7.09 (s, 1H), 7.7 (s, 1H), 8.1 (s, 1H); Mass Spectrum: $M+H^+$ 428.

Example 24

3-cyano-4-[4-(2-cyanoethyl)-2,3-methylenedioxyanilino]-6,7-dimethoxyquinoline

A mixture of 3-[4-(3-cyano-6,7-dimethoxyquinolin-4-ylamino)-2,3-methylenedioxyphenyl]acrylonitrile (0.15 g), 10% palladium-on-carbon (0.025 g), methanol (2 ml) and ethyl acetate (3 ml) was stirred at ambient temperature under an atmosphere pressure of hydrogen for 12 hours. DMF (1.5 ml) was added and reaction mixture was stirred under an atmosphere pressure of hydrogen for a further 12 hours. The mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of hexane and ethyl acetate as eluent. The material so obtained was triturated under diethyl ether. There was thus obtained the title compound as a solid (0.085 g); NMR Spectrum: ($DMSOd_6$) 2.75-2.89 (m, 4H), 3.91 (s, 3H), 3.93 (s, 3H), 5.99 (s, 2H), 6.78-6.88 (m, 2H), 7.3 (s, 1H), 7.75 (s, 1H), 8.43 (s, 1H), 9.46 (s, 1H); Mass Spectrum: $M+H^+$ 403.

The 3-[4-(3-cyano-6,7-dimethoxyquinolin-4-ylamino)-2,3-methylenedioxyphenyl]acrylonitrile used as a starting material was prepared as follows :-

A mixture of 3-cyano-4-(4-iodo-2,3-methylenedioxyanilino)-6,7-dimethoxyquinoline (0.2 g), acrylonitrile (0.2 ml), triethylamine (0.2 ml), palladium(II) acetate (0.01 g) and DMF (2 ml) was stirred and heated to 115°C for 3 hours. The reaction mixture was evaporated and the residue was purified by column chromatography on silica using increasingly polar mixtures of hexane and ethyl acetate as eluent. The material so obtained was triturated under diethyl ether. There was thus obtained the required starting material, in the form of a 4:1 mixture of trans and cis isomers and as a yellow solid (0.095 g); NMR Spectrum: ($DMSOd_6$, data relating to the major trans isomer) 3.91 (s, 3H), 3.93 (s, 3H), 6.12 (s, 2H), 6.26 (d, 1H), 6.88 (d, 1H), 7.14 (d, 1H), 7.35 (s, 1H), 7.56 (d, 1H), 7.7 (s, 1H), 8.51 (s, 1H), 9.7 (s, 1H); Mass Spectrum: $M+H^+$ 401.

Example 25

3-cyano-4-(5-cyano-2,3-methylenedioxyanilino)-6,7-dimethoxyquinoline

Using an analogous procedure to that described in Example 19 except that the reaction mixture was heated to 110°C for 4 hours, 4-(5-bromo-2,3-methylenedioxyanilino)-3-cyano-6,7-dimethoxyquinoline (0.25 g) was reacted with zinc cyanide (0.082 g) to give the title compound as a solid (0.14 g); NMR Spectrum: ($DMSOd_6$) 3.94 (s, 3H), 3.95 (s, 3H), 6.15 (s,

2H), 7.35 (d, 1H), 7.39 (d, 1H), 7.44 (s, 1H), 7.75 (s, 1H), 8.53 (s, 1H), 9.71 (s, 1H); Mass Spectrum: $M+H^+$ 375.

Example 26

3-cyano-6,7-dimethoxy-4-(2,3-ethylidenedioxyanilino)quinoline

Using an analogous procedure to that described in Example 1, 4-chloro-3-cyano-6,7-dimethoxyquinoline was reacted with 2,3-ethylidenedioxyaniline to give the title compound; NMR Spectrum: ($DMSOd_6$) 1.55 (d, 3H), 3.95 (s, 3H), 3.96 (s, 3H), 6.34 (q, 1H), 6.75-6.9 (m, 3H), 7.3 (s, 1H), 7.75 (s, 1H), 8.2 (s, 1H), 9.45 (s, 1H); Mass Spectrum: $M+H^+$ 364.

The 2,3-ethylidenedioxyaniline used as a starting material was prepared as follows :-

A mixture of 3-nitrocatechol (J. Heterocyclic Chem., 1991, 28, 625; 1.6 g), 1,1-dibromoethane (1.4 ml), caesium carbonate (5 g) and DMF (30 ml) was stirred and heated to 110°C for 1 hour. Further quantities of caesium carbonate (5 g) and 1,1-dibromoethane (1.4 ml) were added every hour for a further 5 hours and the resultant mixture was stirred at 110°C for a further 0.5 hours. The mixture was cooled to ambient temperature and partitioned between ethyl acetate and water. The organic phase was washed with a saturated brine solution, dried over sodium sulphate and evaporated. The residue was purified by column chromatography using a 9:1 mixture of isohexane and ethyl acetate as eluant. There was thus obtained 2,3-ethylidenedioxy-1-nitrobenzene as a yellow solid (0.853 g); NMR Spectrum: ($CDCl_3$) 1.8 (d, 3H), 6.5 (q, 1H), 6.9 (t, 1H), 7.0 (d, 1H), 7.58 (d, 1H).

A mixture of the material so obtained, 10% palladium-on-carbon (0.083 g) and ethyl acetate (33 ml) was stirred at ambient temperature under an atmosphere pressure of hydrogen for 3 hours. The catalyst was removed by filtration and the solvent was evaporated. There was thus obtained 2,3-ethylidenedioxyaniline (0.683 g) as an oil; NMR Spectrum: ($CDCl_3$) 1.68 (d, 3H), 3.5 (s, 2H), 6.2 (q, 1H), 6.28 (d, 2H), 6.63 (t, 1H).

Example 27

3-cyano-6,7-dimethoxy-4-(2,3-propylidenedioxyanilino)quinoline

Using an analogous procedure to that described in Example 1, 4-chloro-3-cyano-6,7-dimethoxyquinoline was reacted with 2,3-propylidenedioxyaniline to give the title compound; NMR Spectrum: ($DMSOd_6$) 0.95 (t, 3H), 1.9 (m, 2H), 3.7 (s, 3H), 4.03 (s, 3H),

6.07 (t, 1H), 6.62 (d, 1H), 6.67 (s, 1H), 6.7 (d, 1H), 6.8 (t, 1H), 6.98 (s, 1H), 7.35 (s, 1H), 8.63 (s, 1H); Mass Spectrum: $M+H^+$ 378.

The 2,3-propylidenedioxyaniline used as a starting material was prepared as follows :-

A mixture of 3-nitrocatechol (1.3 g), 1,1-dichloropropane (1.35 ml), caesium carbonate (4.4 g) and DMF (27 ml) was stirred and heated to 90°C for 1 hour. Maintaining this reaction temperature, further quantities of caesium carbonate (4.4 g) and 1,1-dichloroethane (1.35 ml) were added every hour for a further 14 hours and, in addition, potassium bromide (2.5 g) was added after 4 hours and 7 hours respectively. The resultant mixture was cooled to ambient temperature and partitioned between ethyl acetate and water. The organic phase was washed with a saturated brine solution, dried over sodium sulphate and evaporated. The residue was purified by column chromatography using a 9:1 mixture of isohexane and ethyl acetate as eluant. There was thus obtained 2,3-propylidenedioxy-1-nitrobenzene as a yellow solid (0.126 g); NMR Spectrum: ($CDCl_3$) 1.1 (t, 3H), 2.1 (m, 2H), 6.37 (t, 1H), 6.88 (t, 1H), 7.0 (d, 1H), 7.58 (d, 1H).

A mixture of the material so obtained, 10% palladium-on-carbon (0.011 g) and ethyl acetate (5 ml) was stirred at ambient temperature under an atmosphere pressure of hydrogen for 3 hours. The catalyst was removed by filtration and the solvent was evaporated. There was thus obtained 2,3-ethylidenedioxyaniline (0.1 g) as an oil; NMR Spectrum: ($CDCl_3$) 1.1 (t, 3H), 1.98 (m, 2H), 3.5 (s, 2H), 6.05 (t, 1H), 6.28 (2d, 2H), 6.62 (t, 1H).

Claims

1. A combination comprising an inhibitor of the Src family of non-receptor tyrosine kinases, or a pharmaceutically-acceptable salt thereof, and gemcitabine for use in the synergistic treatment or prophylaxis of cancer.

2. A combination as claimed in claim 1 wherein the Src inhibitor is :-
4-(6-chloro-2,3-methylenedioxyanilino)-7-(2-pyrrolidin-1-ylethoxy)-5-tetrahydropyran-4-yloxyquinazoline;
or a pharmaceutically-acceptable acid-addition salt thereof.

3. A combination as claimed in claim 1 wherein the Src inhibitor is :-
4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline;
or a pharmaceutically-acceptable acid-addition salt thereof.

4. A combination as claimed in claim 1 wherein the Src inhibitor is :-
4-(6-chloro-2,3-methylenedioxyanilino)-7-(2-piperidinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline;
or a pharmaceutically-acceptable acid-addition salt thereof.

5. A combination as claimed in claim 1 wherein the Src inhibitor is :-
6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-morpholinopropoxy)quinazoline;
or a pharmaceutically-acceptable acid-addition salt thereof.

6. A combination as claimed in claim 1 wherein the Src inhibitor is :-
4-(2-chloro-5-methoxyanilino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline;
or a pharmaceutically-acceptable acid-addition salt thereof.

7. A combination comprising an inhibitor of the Src family of non-receptor tyrosine kinases, or a pharmaceutically-acceptable salt thereof, and gemcitabine as claimed in claim 1 for use in the synergistic treatment or prophylaxis of pancreatic cancer.

8. A pharmaceutical composition for use in the synergistic treatment or prophylaxis of cancer which comprises a combination as defined in claim 1 in association with a pharmaceutically-acceptable excipient or carrier.

9. The use of a combination as defined in claim 1 in the manufacture of a medicament for administration to a warm-blooded animal such as man to provide the synergistic treatment or prophylaxis of cancer.

10. A method for the synergistic treatment or prophylaxis of cancer which comprises the administration to a warm-blooded animal such as man that is in need of such treatment of effective amounts of the components of the combination as defined in claim 1.

A B S T R A C T

TITLE : COMBINATION PRODUCT

The invention concerns a combination product comprising an inhibitor of Src kinase and the cytotoxic agent gemcitabine, a pharmaceutical composition comprising such a combination and its use in the treatment or prophylaxis of cancer, particularly pancreatic cancer.